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PATENT SPECIFICATION

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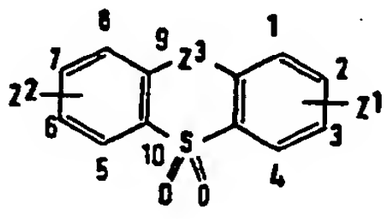
(54) TRICYCLIC SULPHONES AND PHARMACEUTICAL COMPOSITIONS CONTAINING THEM

(71) We, THE WELLCOME FOUNDATION LIMITED, of 183—193 Euston Road, London N.W.1 2BP, a company incorporated in England, do hereby declare the invention for which we pray that a Patent may be granted to us and the method by which it is to be performed, to be particularly described in and by the following statement:—

The invention relates to tricyclic compounds having medicinal properties, the synthesis of the compounds and their adaptation for medicinal use.

It has been found that tricyclic compounds of formula (I), as defined hereinbelow, are active in mammals and in *in vitro* mammalian preparations as inhibitors of allergic reactions associated with reaginic antibodies of the kind responsible for asthma in man, and that this effect is attributable to the suppression of the release of anaphylactic mediators.



(I)

In formula (I) Z^1 is a substituent in the 1-, 2-, 3-, or 4- position and is carboxyl; Z^2 is hydrogen or a substituent in the 5-, 6-, 7-, or 8-position selected from carboxyl, alkylsulphonyl, alkylsulphinyl, alkylthio, amino, alkanoylamino, nitro, cyano, halogen (preferably chlorine or bromine), alkanoyl, alkyl or alkoxy wherein the "alkyl" moiety of each of the alkanoyl, alkyl, alkoxy, alkylthio, alkanoylamino, alkylsulphinyl and alkylsulphonyl groups has 1 to 6 carbon atoms; and

Z^3 represents a bond or is carbonyl, oxygen, sulphur, sulphoxide or methylene;

together with salts of said compounds and when at least one of Z^1 and Z^2 is a carboxyl group, esters and amides of said compounds, provided that when Z^3 is carbonyl and Z^1 is in the 2-position then Z^2, when a substituent in the 5-, 6- or 7-position, is other than halogen, alkanoyl, alkyl, alkoxy, alkylthio, alkylsulphinyl and alkylsulphonyl.

The inhibition activity of the compounds of formula (I) has been demonstrated (a) in tests using the response of passive cutaneous anaphylaxis (PCA test) in which is measured the skin reaction produced as the result of interaction between specific antigen injected intravenously and cell-fixed reaginic antibody previously injected into the skin of a mammal (see for example Z. Ovary: Fedn. Proc. Am. Soc. exp. Biol. *24*, 94 (1965)), (b) by measurement of the amount of histamine released after antigen challenge of peritoneal mast cells from actively sensitised rats (see for example, 1. Acta Pharmacol. et Toxicol. *30*, supp. 1 (1971), 2. Thorax, *27/1*, 38 (1972)), and (c) by measurement of the histamine released from human chopped lung tissue passively sensitised *in vitro* with reaginic antibody when challenged with the homologous antigen (Br. Med. J. *3*, 272 (1968)). The activity of acids

of formula (I) has been demonstrated as described hereinabove using solutions of the anion.

For the sake of convenience, compounds of formula (I) wherein either of Z^1 and Z^2 is or both are an alkyl carboxylate group, are hereinafter referred to as "esters" of formula (I). Similarly references to "amides" of formula (I) shall be constructed as references to compounds of formula (I) wherein one or both of Z^1 and Z^2 is an optionally substituted carboxamide, and references to "salts" of formula (I) shall mean salts of formula (I) wherein one or both of Z^1 and Z^2 is a salt of the acid.

Pharmaceutically acceptable salts of compounds of formula (I) include ammonium salts, alkali metal salts such as sodium and potassium salts, alkaline earth salts such as magnesium and calcium salts, and salts of organic bases, for example, amine salts derived from mono-, di-, or tri-lower alkyl or lower alkanolamines such as triethanolamine and diethylaminoethylamine and salts with heterocyclic amines such as piperidine, pyridine, piperazine and morpholine. Especially valuable for intravenous and pulmonary administration are water soluble salts, most preferably those having a solubility in water of at least 1 mg/ml.

For the purposes of medicinal administration, the carboxylate salt group may be a salt of any pharmaceutically acceptable cation, since the pharmacological activity of the salts is associated with the anion.

Suitable amides includes amides derived from primary or secondary aliphatic amines such as *N*-alkyl and *N,N*-dialkyl amines for example diethylamine. Suitable esters include esters derived from alkyl alcohols. The alkyl moieties of the alkyl esters and *N*-alkyl and *N,N*-dialkyl carboxamides preferably each have 1 to 6 carbon atoms, most desirably 1 to 4 carbon atoms. The amides themselves may be in the form of pharmaceutically acceptable acid addition salts.

Within formula (I) the following preferred subclasses of compounds may be mentioned..

(i) Compounds wherein Z^3 is carbonyl, Z^1 is a substituent in the 3-position and is carboxyl and Z^2 is hydrogen or a substituent in the 5-, 6-, 7- or 8-position selected from carboxyl, nitro, chloro, bromo and alkyl having 1 to 6 carbon atoms, and pharmaceutically acceptable salts thereof;

(ii) Compounds wherein Z^1 is a substituent in the 3-position and is a carboxyl group, a pharmaceutically acceptable carboxylate salt group, an alkyl carboxylate group wherein the alkyl moiety has 1 to 6 carbon atoms, or a carboxamide group optionally *N*-substituted by alkyl having 1 to 6 carbon atoms; Z^2 is hydrogen or a substituent in the 5-, 6-, 7- or 8-position selected from the values of the group Z^1 as defined above or is an alkylsulphonyl group, an alkylsulphinyl group, an alkylthio group, an amino group, an alkanoylamino group, a nitro group, a cyano group, a halogen atom, an alkanoyl group, an alkyl group or an alkoxy group wherein the "alkyl" moiety of each of the alkanoyl, alkyl, alkoxy, alkylthio, alkanoylamino, alkylsulphinyl and alkylsulphonyl groups has 1 to 6 carbon atoms; and Z^3 represents a bond or is carbonyl, oxygen, sulphur, sulphoxide or methylene.

(iii) Compounds wherein Z^2 is hydrogen, Z^3 is as defined in formula (I) and is preferably oxygen or carbonyl, and Z^1 is in the 3-position and is selected from a carboxyl group, a pharmaceutically acceptable carboxylate salt group, an alkyl carboxylate group having 1 to 6 carbon atoms in the alkyl moiety, and a carboxamide group optionally *N*-substituted by an alkyl group having 1 to 6 carbon atoms;

(iv) Compounds wherein Z^3 is as defined in formula (I), Z^1 is in the 3-position, Z^2 is in the 7-position and Z^1 and Z^2 are the same or different and each is selected from a carboxyl group, a pharmaceutically acceptable carboxylate salt group, an alkyl carboxylate group having 1 to 6 carbon atoms in the alkyl moiety, and a carboxamide group optionally *N*-substituted by an alkyl group having 1 to 6 carbon atoms;

(v) Compounds as defined in formula (I) and in any of the foregoing paragraphs (ii), (iii) and (iv) wherein Z^1 is carboxyl, or a pharmaceutically acceptable carboxylate salt group, and especially wherein Z^3 is carbonyl, oxygen or sulphur.

Particularly preferred compounds within formula (I) are:—

(a) 3 - carboxythioxanthone - 10,10 - dioxide;
(b) 2 - carboxyphenoxathiin - 10,10 - dioxide;
(c) 2,6 - dicarboxythioxanthone - 10,10 - dioxide;
(d) 7 - methyl - 3 - carboxythioxanthone - 10,10 - dioxide

and pharmaceutically acceptable salts thereof.

Preferred pharmaceutically acceptable salts of the compounds of formula (I) are the sodium, potassium, magnesium, calcium and ammonium salts. Among salts with an organic base those wherein the base is selected from triethanolamine, diethylaminoethylamine, piperazine and morpholine are preferred.

Within formula (I) a novel subclass is comprised by those compounds wherein Z^1 is a substituent in the 1-, 2-, 3-, or 4- position and is carboxyl, a carboxylate salt group, an alkyl carboxylate group having 1 to 6 carbon atoms in the alkyl moiety, or a carboxamide group optionally N-substituted by alkyl having 1 to 6 carbon atoms;

Z^3 represents a bond or is carbonyl, oxygen, sulphur, sulphoxide or methylene; and

Z^1 is hydrogen or a substituent in the 5-, 6-, 7- or 8-position selected from a carboxylate salt group, alkylsulphonyl, alkylsulphinyl, alkylthio, amino, alkanoylamino, nitro, cyano, halogen, alkanoyl, alkyl, and alkoxy wherein the "alkyl" moiety of each of the alkanoyl, alkyl, alkoxy, alkylthio, alkanoylamino, alkylsulphonyl and alkylsulphinyl groups has 1 to 6 carbon atoms; provided that when Z^2 is hydrogen or a carboxylate salt group then Z^1 is always a carboxylate salt group and the compounds of formula (I) are in the solid state, and provided that, when Z^3 is carbonyl and Z^1 is in the 2-positon then Z^2, when a substituent in the 5-, 6- or 7-position, is other than halogen, alkanoyl, alkyl, alkoxy, alkylthio, alkylsulphinyl and alkylsulphonyl, and except for 7 - nitro - 2 - carboxythioxanthone - 10,10 - dioxide and its amide, 9 - nitro - 4 - carboxyphenoxathiin - 10,10 - dioxide, 8 - chloro - 2 - carboxyphenoxathiin - 10,10 - dioxide and its methyl ester, 4,6 - dicarboxydibenzothiophene - 5,5 - dioxide disodium salt, and 8 - chloro - 2 - carboxythioxanthone - 10,10 - dioxide.

Of the remaining compounds within formula (I) (i.e. those outside of the above-recited subclass) many have been described in the literature as intermediates for the synthesis of derivatives thereof but no biological activity has been previously ascribed to them.

Amongst the novel subclass of compounds of formula (I) as above defined the following preferred classes may be mentioned.

(i) Compounds wherein Z^1 is in the 3-position and is, preferably, carboxyl or a carboxylate salt group.

(ii) Compounds wherein Z^3 is oxygen, carbonyl or sulphur.

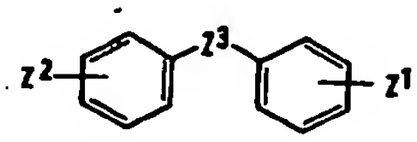
Also preferred are compounds in the solid state wherein Z^1 is a substituent in the 1-, 2-, 3-, or 4-position and is a pharmaceutically acceptable carboxylate salt group; Z^2 is hydrogen or a substituent in the 5-, 6-, 7-, or 8-position selected from a pharmaceutically acceptable carboxylate salt group, alkylsulphonyl, alkylsulphinyl, alkylthio, amino, alkanoylamino, nitro, cyano, halogen, alkanoyl, alkyl and akoxy wherein the "alkyl" moiety of each of the alkyl, alkanoyl, alkoxy, alkylthio, alknoylamino, alkylsulphinyl and alkylsulphonyl groups has 1 to 6 carbon atoms; and Z^3 represents a bond or is carbonyl, oxygen, sulphur, sulphoxide or methylene; provided that, when Z^3 is carbonyl and Z^1 is in the 2-position then Z^2, when a substituent in the 5-, 6- or 7-position, is other than halogen, alkanoyl, alkyl, alkoxy, alkylthio, alkylsulphinyl and alkylsulphonyl, and except for 4,6-dicarboxydibenzothiophene - 5,5 - dioxide disodium salt.

Within the last recited class of compounds those wherein Z^2 is hydrogen are particularly preferred.

Especially preferred are salts of 3 - carboxythioxanthone - 10,10 - dioxide in the solid state, particularly pharmaceutically acceptable salts thereof such as the sodium, potassium and ammonium salts and most of all the sodium salt.

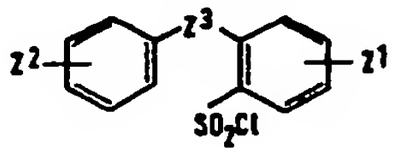
The compounds of formula (I) may be prepared by known chemical techniques. In general, the methods include cyclisation wherein the central ring is completed by ring closure, hydrolysis, oxidation or reduction of precursors leading to both of the groups Z^1 and Z^2 by a variety of techniques. Examples of the preparation of certain compounds of formula (I) by these methods are described at the end of this specification. These general synthetic procedures are also applicable in some instances to the preparation of intermediates.

The cyclisation preparative methods in general include the formation as the final step of one or both of the bridges of the central ring. For example compounds of formula (XIII) wherein Z^1, Z^2 and Z^3 are defined in formula (I), may be reacted



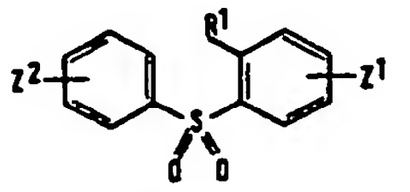
(XIII)

with chlorosulphonic acid to provide corresponding compounds of formula (I), or using chlorosulphonyl compounds of formula (XIV) wherein Z^1, Z^2 and Z^3 are defined in formula (I), the corresponding compounds of formula (I) may be prepared, by ring closure using a Lewis acid, for example aluminium trichloride with heat.



(XIV)

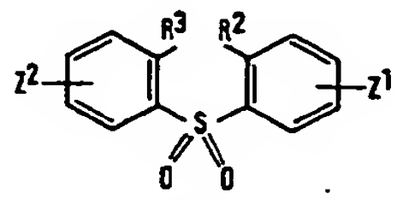
Reaction of a Lewis acid or a protonic acid with substituted diphenyl sulphones of formula (XV) wherein Z^1 and Z^2 are defined in formula (I) and R^1 is a carboxyl group, a derivative thereof such as a nitrile, amide or acid chloride, or an aldehyde produces the thioxanthone - 10,10 - dioxides (in formula (I) Z^3 is carbonyl).



(XV)

Preferred protonic acids are polyphosphoric acid (tetraphosphoric acid), and sulphuric acid. Suitable Lewis acids include aluminium trichloride and boron trifluoride. The reaction is

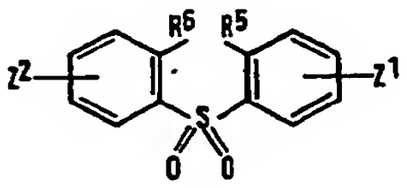
preferably carried out at a temperature from 50° to 300°C. Compounds of formula (I) wherein Z^3 is oxygen or sulphur may be prepared by cyclisation from a sulphone of formula (XVI) wherein



(XVI)

Z^1 and Z^2 are defined in formula (I), one of R^2 and R^3 is a leaving group euch as halo, nitro or sulphinyl, and the other is a mercapto, hydroxy or ester thereof, by reaction with a base such as an alkali metal alkoxide, for example sodium methoxide.

Thianthrene - 10,10 - dioxides may also be prepared by reacting a compound of formula (XVII) wherein Z^1 and Z^2 are defined in formula (I) and R^5 and R^6 are the same or different and each is



(XVII)

a leaving group such as halo, nitro or sulphinyl, with sodium sulphide.

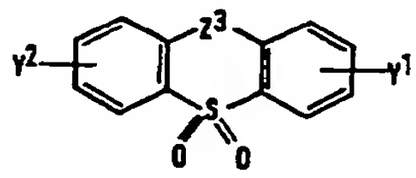
These cyclisation reactions may also be used to provide intermediates which can then be converted by methods described below into compounds of formula (I). Thus thioxanthene intermediates may be made by cyclisation of 2,2′ - dihalophenylmethanes in the presence of sodium sulphide: These compounds and the corresponding 9-oxides may also be prepared by cyclisation of 2-sulphonyldiphenylmethane or 2 - phenylthiobenzaldehydes in the presence of sulphuric acid.

A variety of oxidation techniques may be used to prepare the compounds of formula (I) by completion of one or both of the bridges of the central ring. For example, the thioxanthone - 10,10 - dioxides (in formula (I), Z^3 is carbonyl) may be prepared by oxidation of the corresponding thioxanthene - 10,10 - dioxides (in formula (I), Z^3 is methylene), using for example Triton B, pyridine and oxygen (" Triton " is a Registered Trade Mark). Compounds of formula (I) may also be prepared by oxidation of the corresponding sulphoxides and sulphides to form the sulphones, using for example hydrogen peroxide and acetic acid. In the case of thianthrenes and thianthrene - 10 - oxides, the thianthrene - 9,10,10 - trioxides are produced.

Reduction methods may also be employed to make the thioxanthene - 10,10 - dioxides of formula (I) from the corresponding thioxanthone - 10,10 - dioxides using appropriate reducing agents such as zinc and an acid, for example acetic or hydrochloric acid. Reduction of thianthrene - 9,10,10 - trioxides with appropriate reducing agents such as zinc and an acid, for example hydrochloric or acetic acid, yields the corresponding thianthrene - 10,10 - dioxides.

The compounds of formula (I) may also be prepared by formation of one or both of the groups Z^1 and Z^2 as the final step.

The compounds of formula (I), wherein Z^1 or both Z^1 and Z^2 are carboxyl may also be prepared by a variety of methods which include as the final step the formation of the carboxyl group(s). The compounds may be isolated as the free acid, as salts thereof, or converted to amides or esters of formula (I), depending upon the nature of the desired products. Thus they may be prepared by hydrolysis of a compound of formula (XIX)

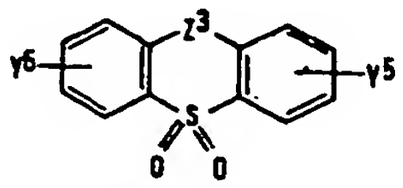


(XIX)

wherein Y^1 is a carboxyl group precursor or a group Z^1 as defined in formula (I), Y^2 is a carboxyl group precursor or a group Z^2 as defined in formula (I), where the carboxyl group precursor may in each case be such as a nitrile group, trichloromethyl group or a group COL^1 wherein L^1 is a leaving group, such as a nucleophilic atom or group, for example, a trichloromethyl group, an optionally substituted amino group, a halogen atom or an alkoxy group, and provided that at least one of Y^1 and Y^2 is a carboxyl group precursor; and Z^3 has the meaning defined in formula (I). Hydrolysis is conveniently effected by heating a compound of formula (XIX) with a base or a dilute aqueous mineral acid optionaly with an organic acid. For example, one may use dilute sulphuric acid or dilute hydrochloric acid with acetic acid, or a base such as an aqueous alkali metal hydroxide or alkoxide. Basic conditions are, however, undesirable in the preparation of the thioxanthone - 10,10 - dioxides.

By means of nucleophilic substitution reactions analogous to hydrolysis, for example, alcoholysis and ammonolysis, esters and amides of formula (I) may be prepared directly from compounds of formula (XIX). Thus reaction of a compound of formula (XIX) with an appropriate alcohol yields an ester of formula (I), and reaction with ammonia or an appropriate primary or secondary amine yields an amide of formula (I).

The carboxylic acids of formula (I) and their salts may also be made by oxidation of a compound of formula (XX) wherein Y^5 is an alkyl group, an alkanoyl group or a group Z^1 as defined in formula (I), Z^3 is as defined in formula (I),

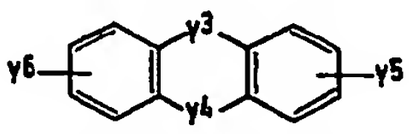


(XX)

and Y^6 is an alkyl group, an alkanoyl group or a group Z^3 as defined in formula (I) provided that at least one of Y^5 and Y^6 is an alkyl or alkanoyl group. Oxidation of compounds wherein Y^5 and/or Y^6 are lower alkyl groups may be effected with such conventional oxidising agents as acid or alkaline aqueous potassium permanganate solution; chromium trioxide, for example; with acetic acid or sulphuric acid; oxygen in the presence of a convention catalyst such as vanadium, cobalt and manganese salts or oxides; or aqueous solutions of dichromate salts.

Oxidation of compounds wherein Y^5 and/or Y^6 are alkanoyl groups may be effected with such conventional oxidising agents as chromium trioxide, for example, with acetic acid or sulphuric acid; aqueous solutions of salts of hypochlorous and hypobromous acids in the presence of a base; sodium or potassium dichromate with acetic acid; or nitric acid. These oxidation procedures are advantageously effected with heating in a liquid medium.

If desired, oxidative formation of Z^1 and/or Z^2 carboxyl groups, the bridging sulphonyl linkage, and Z^3 sulphoxide or carbonyl linkage, may be carried out either simultaneously or sequentially. Thus compounds of formula (I) may be prepared by oxidation with an appropriate oxidising agent selected from those recited hereinabove of a compound of formula (XXI) wherein Y^5 and Y^6 are each as defined above in formula (XX), Y^3 represents a bond or is carbonyl, oxygen,



(XXI)

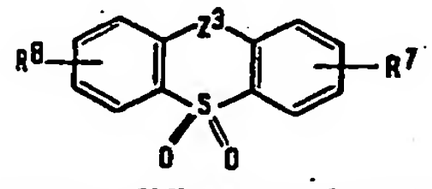
sulphur, sulphoxide, or methylene, and Y^4 is sulphur, sulphoxide or sulphone provided that when Y^5 is the same as Z^1 and Y^6 is the same as Z^2 then at least Y^4 is sulphur or sulphoxide or Y^3 is methylene or sulphur.

It will of course be understood that the oxidative formation of the side chains Z^1 and/or Z^2, the bridging carbonyl and sulphoxide groups Z^3 and the bridging sulphonyl linkage, may be carried out either simultaneously as a one-pot reaction or sequentially, by the use of appropriate oxidising agents.

The foregoing synthetic methods for the preparation of the compounds of formula (I) are preferably effected in a liquid medium. In the operation of these methods, it will be understood that where the groups Z^1 and Z^2 are formed prior to the complete formation of the desired compound, then in some instances Z^1 and/or Z^2 must be protected from inter-reaction in the final synthetic stage or stages; thus for example when Z^2 is an amino group, it may be protected by acylation and the acylamino group subsequently hydrolysed. In other instances it is advisable to form the groups Z^1 and/or Z^2 as the final synthetic step, if the group(s) would react in the final synthetic stage(s).

Pharmaceutically acceptable salts of carboxylic acids of formula (I) are prepared by any conventional method, for example by neutralising the corresponding carboxylic acid with an appropriate Brönsted base, or by double decomposition of a salt of an acid of formula (I) so as to produce the desired salt of an appropriate pharmaceutically acceptable cation. The carboxylic acid may be either the isolated acid, or may be present in solution in the reaction mixture resulting from a preparation of the compound, for example by such a method as described hereinbefore. Suitable Brönsted bases include organic bases such as ethanolamine, and bases containing ammonium, and alkali metal and alkaline earth metal cations. Double decomposition may be effected advantageously in an anion exchange resin wherein a solution of a salt of an acid of formula (I) is passed through a cation exchange resin, the resin being charged with a pharmaceutically acceptable cation of the suitable base. Double decomposition may also be effected in ordinary solution between a salt of an acid of formula (I) and a salt of the desired pharmaceutically acceptable cation.

Specifically, pharmaceutically acceptable salts of carboxylic acids of formula (I) may be prepared by reaction in a polar medium of a compound of formula (XXIV) wherein R^7 and R^8



(XXIV)

are the same or different and each is selected from a carboxyl group and a group Y^1 or Y^2, as appropriate, as defined hereinbefore in formula (XIX), and Z^3 has the meaning in formula (I), with an appropriate Brönsted base and, when the Brönsted base does not contain a hydroxyl ion, in the presence of water. Examples of appropriate Brönsted bases are alkali and alkaline earth metal oxides and hydroxides for producing corresponding alkali and alkaline earth metal salts of formula (I). Preferably the reaction is effected with heating.

Salts of formula (I) may be isolated from a reaction medium by any conventional process for the isolation of salts from a solution thereof in a polar medium. Thus the salts may be isolated by precipitation of the salt or by removal of the polar medium.

Precipitation of the salt may be effected by mixed solvent crystallisation or by the addition of excess of base or salt thereof so as to produce a concentration of the cation of the salt to be isolated, substantially in excess of the molar ratio thereof in said salt to be isolated.

Mixed solvent crystallisation may be effected by addition, to a solution of a salt of formula (I) in a polar medium, of a second solvent miscible with the solvent already present and in which second solvent the salt of formula (I) is less soluble than in the solvent already present.

Removal of the polar medium may be effected by evaporation, for example, by freeze-drying, or by azeotropic distillation.

Desirably the salts of formula (I) are purified prior to incorporation in a pharmaceutical composition. Purification may be effected by any conventional method. A particularly valuable purification process comprises isolation of a crude solid salt of formula (I) from a reaction mixture wherein said salt has been produced, by any method for the isolation of salts of formula (I) as described hereinabove; treatment of an aqueous solution of salt with hydrochloric acid; recovery of the corresponding acid of formula (I) as solid; neutralisation of the acid of formula (I) with Brönsted base of which base the cation is the cation of the required salt of formula (I), removal of solid impurities by filtration; and isolation of the salt of formula (I) by a method as described hereinabove.

Conveniently a carboxylic acid of formula (I) may be purified prior to neutralisation, by recrystallisation or by isolation of an *N,N*-dimethylformamide adduct and subsequently heating the adduct to drive off the *N,N*-dimethylformamide. Recrystallisation may be effected using a polar organic solvent optionally containing water, for example, aqueous dimethylformamide, aqueous acetone, or acetic acid may be used.

Esters and amides of acids of formula (I) may be prepared by any conventional method including esterification of the acid or acid chloride with an alkyl or aryl alcohol to yield the corresponding alkyl or aryl esters respectively and reaction of the acid or acid chloride with ammonia or an amine to yield the corresponding amide or substituted amide respectively. Compounds of formula (I) where Z^1 and Z^2 are different and are chosen from acid, ester, amide and salt functions, may be prepared by the above methods, and by partial hydrolysis, where appropriate.

The compounds of formula (I) are useful in the treatment of prophylaxis of mammalian allergic conditions such as asthma and other allergic chest conditions, hay fever (allergic rhinitis), conjunctivitis, urticaria and eczema.

In particular they are of value in reaginic mediated Type I hypersensitivity asthma ("extrinsic asthma") and the so-called "intrinsic asthma" in which no sensitivity to extrinsic antigen can be shown.

The magnitude of a prophylactic or therapeutic dose of compound of formula (I) will of course vary with the nature and the severity of the allergic condition to be treated and with the particular compound of formula (I) and its route of administration. In general the dose range lies within the range of 2 μg. to 100 mg. per Kg. body weight of a mammal.

In the case of an allergic condition as defined hereinbefore, for example, allergic asthma, a suitable dosage is from 5 μg. to 0.5 mg., preferably from 20 μg. to 0.2 mg., for example about 0.1 mg., of a compound of formula (I), per Kg. of bodyweight of the patient undergoing treatment, when pulmonary administration as described hereinafter is employed. In the case where a composition for intravenous administration is employed a suitable dosage range is from 0.2 to 10 mg. (preferably 1 to 5 mg.) of a compound of formula (I) per Kg. of body weight of patient, and in the case where an oral composition is employed a suitable dosage range is from 1 to 50 mg. of a compound of formula (I) per Kg. of bodyweight of a patient, preferably from 10 to 40 mg/Kg.

In the case where a composition for nasal and ocular administration is employed, for example, in the treatment of allergic rhinitis, a suitable dose is from 0.5 to 25 mg. of a compound of formula (I) per patient.

The pharmaceutical compositions of the present invention comprises a compound of formula (I) as an active ingredient in association with a pharmaceutically acceptable carrier therefore and optionally other therapeutic ingredients. The compositions include compositions suitable for oral, rectal, opthalmic, pulmonary, nasal, dermal, topical, or parenteral (including subcutaneous, intramuscular and intravenous) administration, although the most suitable route in any given case will depend on the nature and severity of the condition being treated, and on the nature of the active ingredient. They may be conveniently presented in unit dosage form and prepared by any of the methods well known in the art of pharmacy.

Pharmaceutical compositions of the present invention suitable for oral administration may be presented as discrete units such as capsules, cachets or tablets, for example, a moisture resistant formulation such as a coated tablet or in a capsule, each containing a predetermined amount of the active ingredient; as a powder or granules; or as a solution or a suspension in an aqueous liquid, a non-aqueous liquid, an oil-in-water emulsion or a water-in-oil liquid emulsion. Such compositions may be prepared by any of the methods of pharmacy but all methods include the step of bringing

into association the active ingredient with the carrier which constitutes one or more accessory ingredients. In general the compositions are prepared by uniformly and intimately admixing the active ingredient with liquid carriers or finely divided solid carriers or both, and then, if necessary, shaping the product into the desired presentation. For example a tablet may be prepared by compression or moulding, optionally with one or more accessory ingredients. Compressed tablets may be prepared by compressing in a suitable machine, the active ingredient in a free-flowing form such as a powder or granules, optionally mixed with a binder, lubricant, inert diluent, lubricating, surface active or dispersing agent. Moulded tablets may be made by moulding in a suitable machine, a mixture of the powdered compound moistened with an inert liquid diluent. Desirably, each tablet contains from 50 mg to 500 mg of the active ingredient, and each cachet or capsule contains from 50 to 500 mg of the active ingredient.

A particularly valuable form of a pharmaceutical composition of the present invention, for use in the treatment of allergic asthma, is a composition suitable for pulmonary administration *via* the buccal cavity; although of course conditions other than allergic asthma may also be treated by pulmonary administration of the composition.

Preferably the composition is such that particles having a diameter of 0.5 to 7μ, most preferably 1 to 6μ, containing active ingredient, are delivered into lungs of a patient. This ensures that a maximal amount of active ingredient is administered to the alveolar sacs of the lung and retained therein thus producing a maximal effect in the patient. Such compositions are most preferably in the form of finely comminuted powders for pulmonary administration from a powder inhalation device or self-propelling powder-dispensing compositions, where the tricyclic compound (active ingredient) finely comminuted powder may comprise up to 99.9% w/w of the composition.

Most preferably the powders of the pulmonary compositions as described hereinabove and hereinbelow comprise particles containing active ingredient of which particles at least 98% by weight have a diameter greater than 0.5μ and at least 95% by number have a diameter less than 7μ. Most desirably at least 95% by weight of the particles have a diameter greater than 1μ and at least 90% by number of the particles have a diameter less than 6μ.

The compositions in the form of dry powders preferably comprise particles containing the solid active ingredient, the particles having a diameter of 0.5 to 7μ most preferably 1 to 6μ. Preferably these compositions include a solid diluent in the form of a fine powder. These compositions may be conveniently presented in a piercable capsule of a pharmaceutically acceptable material, for example gelatin, for use in an inhalation device. Such compositions may be conveniently prepared by comminution of solid active ingredient optionally with a solid diluent. If desired the resulting powder may be filled into a piercable capsule of a pharmaceutically acceptable material.

Other valuable forms of a composition of the present invention that are suitable for pulmonary administration are self-propelling compositions. These self-propelling compositions may be either powder-dispensing compositions or compositions dispensing the active ingredient in the form of droplets of a solution or suspension.

Self-propelling powder-dispensing compositions preferably comprise dispersed particles of solid active ingredient, having a diameter of 0.5 to 7μ most preferably 1 to 6μ and a liquid propellant having a boiling point of below 65°F (18°C.) at atmospheric pressure. The liquid propellant may be any propellant known to be suitable for medicinal administration and may comprise one or more lower alkyl hydrocarbons, or halogenated lower alkyl hydrocarbons, or mixtures thereof. Chlorinated and fluorinated lower alkyl hydrocarbons are especially preferred as propellant. Generally the propellant may constitute 50 to 99.9% w/w of the composition whilst the active ingredient may constitute 0.1 to 20% w/w, for example, about 2% w/w, of the composition.

The pharmaceutically acceptable carrier in such self-propelling compositions may include other constituents in addition to the propellant, in particular a surfactant or a solid diluent or both. Surfactants are desirable in preventing agglomeration of the particles of active ingredient and in maintaining the active ingredient in suspension. Especially valuable are liquid non-ionic surfactants and solid anionic surfactants or mixtures thereof. Suitable liquid non-ionic surfactants are those having a hydrophile-lipophile balance (HLB, see Journal of the Society of Cosmetic Chemists Vol. 1 pp. 311—326 (1949)) of below 10, in particular esters and partial esters of fatty acids with aliphatic polyhydric alcohols for instance, sorbitan monooleate and sorbitan trioleate, known commercially as "Span 80" (Trade Name) and "Span 85" (Trade Name). The liquid non-ionic surfactant may constitute from 0.01 up to 20% w/w of the composition, though preferably it constitutes below 1% w/w of the composition. Suitable solid anionic surfactants include alkali metal, ammonium and amine salts of dialkyl sulphosuccinate, where the alkyl groups have 4 to 12 carbon atoms, and alkylbenzene sulphonic acid where the alkyl group has 8 to 14 carbon atoms. The solid anionic surfactants may constitute from

0.01 up to 20% w/w of the composition, though preferably below 1% w/w of the composition.

Solid diluents may be advantageously incorporated in such self-propelling compositions where the density of the active ingredient differs substantially from the density of the propellant; also in order to help to maintain the active ingredient in suspension. The solid diluent is in the form of a fine powder, preferably having a particle size of the same order as that of the particles of active ingredients. Suitable solid diluents include sodium chloride, sodium sulphate, and a sugar.

Compositions of the present invention may also be in the form of a self-propelling composition wherein the active ingredient is present in solution. Such self-propelling compositions may comprise an active ingredient, propellant and co-solvent, and advantageously an antioxidant stabiliser. The propellant is one or more of those already cited above. Co-solvents are chosen for their solubility in the propellant, their ability to dissolve the active ingredient, and for their having the lowest boiling point consistent with these above-mentioned properties. Suitable co-solvents are lower alkyl alcohols and ethers and mixtures thereof. The co-solvents may constitute 5 to 40% w/w of the composition, though preferably less than 20% w/w of the composition.

Antioxidant stabilisers may be incorporated in such solution-compositions to inhibit deterioration of the active ingredient and are conveniently alkali metal ascorbates or bisulfites. They are preferably present in an amount of up to 0.25% w/w of the composition.

Such self-propelling compositions may be prepared by any method known in the art. For example the active ingredient either as particles as defined hereinbefore in suspension in a suitable liquid or in up to 20% w/v solution in an acceptable co-solvent as appropriate, is mixed with any other constituents of a pharmaceutically acceptable carrier. The resulting mixture is cooled and introduced into a suitable cooled container and propellant is added thereto in liquid form; and the container is sealed.

Alternatively, such self-propelling compositions may be prepared by mixing the active ingredient either in particles as hereinbefore defined or in 2 to 20% w/v alcohol or aqueous solution as appropriate, together with the remaining constituent of the pharmaceutically acceptable carrier other than propellant; introducing the resulting mixture, optionally with some propellant, into a suitable container, sealing the container; and injecting propellant under pressure into the container at ambient temperature through a valve which comprises a part of the container and is used to control release of the composition from it. Desirably the container is purged by removing air from it at a convenient stage in the preparation of the self-propelling composition.

A suitable container for a self-propelling composition, is one provided with a manually operable valve and being constructed of aluminium, stainless steel or reinforced glass. The valve should of course be one having the desired spray characteristic, that is, the spray issuing from the valve should have the characteristics of particle size as hereinbefore defined. Advantageously the valve is of the metered type, that is a valve of the type which delivers a fixed amount of composition on the occasion of each operation of the valve, for example, about 50 or 100 microlitres of composition in each delivery.

Compositions of the present invention may also be in the form of aqueous or dilute alcoholic solution, optionally a sterile solution, of the active ingredient for use in a nebuliser or atomiser, wherein an accelerated air stream is used to produce a fine mist consisting of small droplets of the solution. Such compositions usually contain a flavouring agent such as saccharin sodium and a volatile oil. A buffering agent such as sodium phosphate; an antioxidant such as sodium metabisulfite; and a surface active agent may also be included in such a composition. Desirably such a composition should contain a preservative such as methylhydroxybenzoate.

Compositions of the present invention suitable for parenteral administration conveniently comprise sterile aqueous solutions of the active ingredient, which solutions are preferably isotonic with blood of a patient under treatment. These are preferably administered intra-venously, although administration may also be effected by means of subcutaneous or intra-muscular injection. Such compositions may be conveniently prepared by dissolving solid active ingredient in water to produce an aqueous solution, and rendering said solution sterile and isotonic with human blood.

Pharmaceutical compositions of the present invention suitable for topical use include compositions suitable for administration to the skin, eyes, nose and mouth.

Compositions for use on the skin include lotions and creams comprising liquid or semi-solid emulsions, either oil-in-water or water-in-oil, which preferably contain from 0.2 to 5% w/v of the active ingredient. Ointments comprising 0.2 to 5% w/v of the active ingredient dissolved or dispersed in a semi-solid basis may also be used for topical administration to the skin. Conveniently the semi-solid basis contains liquid or semi-solid hydrocarbons, animal fat, wool alcohol or a macrogol, possibly with an emulsifying agent. Desirably the creams and ointments should contain a preservative such as methyl hydroxybenzoate.

Compositions for administration to the eye include eye drops comprising the active ingredient in aqueous or oily solution, preferably at a concentration of 0.2 to 5% w/v. Such solutions are desirably fungistatic and bacteriostatic and are preferably prepared sterile. Compositions for administration to the eye also include eye ointments which preferably comprise the same concentration of active ingredient, convenient in the form of a salt, either dissolved in one of the ingredient of the semi-solid basis of the ointment or as a finely divided suspension therein.

Compositions suitable for administration to the nose include powder, self-propelling and spray compositions similar to those already described under compositions suitable for pulmonary administration but having when dispersed, a somewhat larger particle size of the order of 10 to 200 microns. In the case of self-propelling solution and spray compositions this effect may be achieved by choice of a valve having the desired spray characteristic, i.e. being capable of producing a spray having the desired particle size or by incorporating the medicament as a suspended powder of controlled particle size. Thus the composition instead of passing into the lungs is largely retained in the nasal cavity. Other compositions suitable for nasal administration include a coarse powder having a particle size of 20 to 500 microns which is administered in the manner in which snuff is taken, i.e. by rapid inhalation through the nasal passage from a container of the powder held close up to the nose. Another composition suitable for nasal administration is nasal drops comprising 0.2 to 5% w/v of the active ingredient in aqueous or oily solution.

Compositions suitable for topical administration in the mouth include lozenges comprising 10 to 100 mg. of the active ingredient in a flavoured basis, usually sucrose and acacia or tragacanth; and pastilles comprising 10 to 100 mg. of the active ingredient in an inert basis such as gelatin and glycerin; or sucrose and acacia.

Other therapeutic ingredients suitable for inclusion in the hereinbefore described compositions, especially in the case of those compositions intended for use in the treatment of allergic asthma, include bronchodilators. Any bronchodiluator may be used in such a composition although particularly suitable bronchodilators are isoprenaline, adrenaline, orciprenaline, isoethanine and physiologically acceptable acid addition salts thereof, especially isoprenaline sulphate. Conveniently the bronchodilator is present in the composition in an amount of 0.1 to 50% w/w of the weight of active ingredient present.

Included within the scope of the present invention, but in no way limited thereto, are the following specific features: —

1. 3 - Carboxythioxanthone - 10,10 - dioxide salts in the solid state.
2. Novel compounds within formula (I) as defined hereinabove.
3. The synthesis of the novel compounds within formula (I) as defined hereinabove, by any method known in the art for preparing compounds of analogous chemical structure.
4. Pharmaceutical compositions comprising a compound of formula (I) as defined hereinabove in association with a pharmaceutically aceptable carrier therefor.
5. The preparation of pharmaceutical compositions comprising a compound of formula (I) as defined hereinabove as an active ingredient, by any conventional method, including admixture of the ingredients.

The following preparations and Examples illustrate the methods for preparing compounds in accordance with the present invention, as well as compounds and compositions of the present invention. In the Examples and preparations, all temperatures are in degrees Celsius. Where melting points are not given for compounds of formula (I) the compounds decompose at temperatures below their melting points and/or their melting points are at temperatures above those readily determinable by conventional techniques. In these preparations and examples, the numbering of substituent positions in the tricyclic nucleus used is not necessarily the same as that used in formula (I), but is the standard numbering in respect of the particular tricyclic nucleus concerned, as given in the "Ring index", IInd Edition, Published by The American Chemical Society, 1960. This standard numbering also applies in respect of the individual named compounds disclosed hereinbefore.

It should be understood that excluded from the scope of the present invention are non-sterile mixtures which are mere solutions or suspensions of compounds which are within formula (I) but outside of the novel subclass therein as hereinabove defined, in solvents and liquids known in the literature for use in the synthesis and/or isolation of the compounds by the methods described therein. Included within the scope of the present invention are such solutions and suspensions of such compounds which are pharmaceutically acceptable to the intended recipient thereof and which contain in addition at least one other pharmaceutically acceptable substance.

Reference Preparation 1

2 - Carboxydibenzothiophene - 5,5 - dioxide

A. Preparation of 2 - Acetyldibenzothiophene

Dibenzothiophene (18.4 g.) and anhydrous aluminium chloride (13.3 g.) were mechanically stirred in carbon disulphide (100 ml.)

while acetyl chloride (7.85 g.) in carbon disulphide (20 ml.) was added dropwise over 0.5 hr. The temperature of the mixture rose to 30°C. After a total of 4 hr. stirring the mixture was poured onto ice and extracted with chloroform. The extract was washed with sodium bicarbonate solution, dried with magnesium sulphate, and evaporated. The residue was distilled under vacuum and a fraction, b.pt. 160°—180°C at 0.6 mm. Hg, was extracted by boiling with ether, and the residue recrystallised twice from methanol to give colourless crystals of 2 - acetyldibenzothiophene m.pt. 97°—100°C.

B. Preparation of Dibenzothiophene - 2 - carboxylic acid

2 - Acetyldibenzothiophene (2.24 g.), sodium hypochlorite solution, (47 ml. containing 5.7% available chlorine), Normal sodium hydroxide solution (50 ml.) and dioxan (50 ml.), were heated on a steam bath with stirring for 5 hr. The mixture was acidified with excess hydrochloric acid, and the precipitated colourless solid filtered off, washed with water, and recrystallised twice from acetic acid to give dibenzothiophene - 2 - carboxylic acid, m.pt. 281°—283°C.

C. Preparation of 2 - Carboxydibenzothiophene - 10,10 - dioxide

A mixture of dibenzothiophene - 2 - carboxylic acid (0.7 g), 30% hydrogen peroxide (3.0 ml.) and acetic acid (30 ml.) was boiled under reflux for 2.5 hr. The solid product which separated on cooling was filtered off, recrystallised from dimethylformamide, and dried at 110°C, to give 2-Carboxydibenzothiophene - 10,10 - dioxide, m.pt. >350°C.

Found:	C 59.78%, H 3.38%
$C_{13}H_8O_4S$ requires	C 59.98% H 3.10%

Reference Preparation 2

2,8 - Dicarboxyphenoxathiin - 10,10 - dioxide

A. Preparation of 2,8 - Diacetylphenoxathiin - 10,10 - dioxide

2,8 - Diacetylphenoxathiin (10.0 g.) was boiled under reflux for 1 hr. with glacial acetic acid (200 ml.) and 30% hydrogen peroxide (30 ml.). The solution was allowed to cool, and the colourless platelets which crystallised out were filtered off and dried to yield 2,8 - diacetylphenoxathiin - 10,10 - dioxide, m.pt. 219°—220°C.

B. Preparation of 2,8 - Dicarboxyphenoxathiin - 10,10 - dioxide

2,8 - Diacetylphenoxathiin - 10,10 - dioxide (10.9 g.), acetic acid (480 ml.) and chromium trioxide (20.0 g.) were boiled under reflux for 45 min. On cooling the product crystallised out and was filtered off, washed with water, and recrystallised from aqueous dimethylformamide to yield colourless needles of 2,8 - dicarboxyphenoxathiin - 10,10 - dioxide, m.pt. 399°—401°C.
Thin layer chromatography indicated slight contamination with monocarboxylic acid.

Found:
C 53.16%; H 2.60%; S 9.65%
$C_{14}H_8O_7S$ requires:
C 52.51%; H 2.52%; S 9.98%

Reference Preparation 3

2 - Methoxycarbonylphenoxathiin - 10,10 - dioxide

2 - Carboxyphenoxathiin - 10,10 - dioxide (0.50 g.) in carbon tetrachloride (25 ml.) and thionyl chloride (2.0 ml.) was boiled under reflux for 2 hr. The solvent was evaporated and methanol (20 ml.) added. The mixture was boiled under reflux for 20 min., and cooled, whereupon 2 - methoxycarbonylphenoxathiin - 10,10 - dioxide crystallised out and was filtered off and dried, m.pt. 160°C.

Found:	C 57.92%; H 3.47%
$C_{14}H_{10}O_6$ requires:	C 57.92%; H 3.47%

Reference Preparation 4

3 - Carboxythioxathone - 10,10 - dioxide

A. Preparation of 2,5 - dimethyl diphenyl sulphone

To a mixture of benzene sulphonyl chloride (redistilled) (100.0 g.) and *p*-xylene (260 ml), vigorously stirred and heated to 40°C, was added aluminium chloride (135 g.) portionwise over 20 minutes. The temperature of the reaction was kept between 55° and 60°C during the addition by means of an ice-bath. The reaction was maintained at 60°C for a further 45 minutes, cooled and decomposed with ice and concentrated hydrochloric acid. The product separated from the organic layer as a yellow solid. This was filtered off, washed with water, and recrystallised from methanol. The resulting solid was collected by filtration, washed with a little cold methanol, and dried at 95°C to give 2,5 - dimethyl diphenyl sulphone melting point 111°C.

B. Preparation of diphenyl sulphone - 2,5 - dicarboxylic acid

2,5 - Dimethyl diphenyl sulphone (106 g.), concentrated nitric acid (400 ml) and distilled water (400 ml) were placed in a stainless steel autoclave, sealed, stirred and heated to 160°C for a total of 5 hours. The internal pressure rose to ca. 75 atmospheres. After cooling, the crystalline product was collected by filtration, washed well with water, and dried at 100°C. The resulting diphenyl sulphone - 2,5 - dicarboxylic acid had a melting point of 270—274°C.

C. Preparation of 3 - carboxythioxathone - 10,10 - dioxide

Diphenyl sulphone - 2,5 - dicarboxylic acid (156.8 g.) was stirred with tetraphosphoric acid (ca. 3,300 g.) and phosphorus pentoxide (ca. 330 g.) at 220 to 230°C for 20 minutes, cooled, and poured onto ice-water with stirring. The precipitated solid was filtered off under suction, washed well with water and dried at 100°C. The total product was recrystallised from aqueous dimethyl formamide, filtered at the boil. The product separated as beige crystals. These were first dried at 100°C, then under vacuum at ca. 170°C, to give 3 - carboxythiaxanthone - 10,10 - dioxide having a melting point of 287—289°C.

Reference Preparation 5

2 - Carboxyphenoxathiin - 10,10 - dioxide

A. Preparation of 2 - acetylphenoxathiin

Phenoxathiin (22.9 g) and acetyl chloride (8.8 ml) were dissolved in carbon disulphide (120 ml) and mechanically stirred while aluminium chloride (15.5 g) was added in small portions. The red mixture was stirred for 2 hr. at room temperature, then boiled under reflux on the water bath for a further 2-1/4 hr. The mixture was cooled and poured on to ice and hydrochloric acid, and the precipitated product filtered off, washed with water, and recrystallised once from ethanol and twice from petroleum ether (b.p. 80°—100°C) to give the product m.p. 112°C.

B. Preparation of phenoxathiin - 2 - carboxylic acid

A mixture of 2 - acetylphenoxathiin (4.80 g), sodium hypochlorite solution (95 ml; 5.7% available chlorine), 4% sodium hydroxide solution (100 ml) and dioxan (100 ml) was mechanically stirred on the steam bath for 5 hrs. The solution was poured on to ice and excess hydrochloric acid with stirring. The white precipitate was filtered off and dissolved in hot 4% sodium hydroxide solution (40 ml) and filtered. The sodium salt of the required acid crystallised from the filtrate on cooling and was filtered off, dissolved in boiling water, and the acid precipitated by addition of excess hydrochloric acid. It was filtered off and recrystallised from acetic acid, m.p. 253°C.

C. Preparation of 2 - carboxyphenoxathiin - 10,10 - dioxide

Phenoxathiin - 2 - carboxylic acid (3.50 g) was boiled with 30% hydrogen peroxide (10 ml) in acetic acid (100 ml) for 2.5 hr. On cooling the product crystallised out and was filtered off and dried, m.p. 286°C.

Reference Preparation 6

2 - Carboxythioxanthone - 10,10 - dioxide

A. Preparation of diphenylsulphone - 2,4 - dicarboxylic acid

Diphenylsulphone - 2,4 - dicarboxylic acid was obtained (in the manner described above in preparation 4B by the method used for diphenyl - 2,5 - dicarboxylic acid) as colourless needles from water, m.p. 246°C.

B. Preparation of 2 - Carboxythioxanthone - 10,10 - dioxide

Diphenylsulphone - 2,4 - dicarboxylic acid (10.5 g) was stirred and heated with polyphosphoric acid (200 g) at 210—220°C for 15 minutes, cooled, and poured into water. On heating the mixture to 80°C the crude product separated and was filtered off and recrystallised from acetic acid, m.p. 276°C.

Reference Preparation 7

2 - Carboxythioxanthone - 10,10 - dioxide

A. Preparation of methylthioxanthone (isomer mixture)

To a stirred mixture of concentrated sulphuric acid (300 ml) and toluene (46 ml), o-mercaptobenzoic acid (30 g) was added slowly. The mixture was stirred for 8 hrs. and allowed to stand for a further 10 hrs. After 1 hr. heating on the steam bath the dark red solution was cooled and poured on to ice. The gummy yellow precipitate was filtered off and triturated with 2N aqueous sodium hydroxide. The solid isomer-mixture was filtered off, washed with water, and dried at room temperature *in* vacuo, m.p. 107°—132°C.

B. Preparation of 2 - methylthioxanthone - 10,10 - dioxide

To the methylthioxanthone isomer mixture (30.3 g) dissolved in warm acetic acid (200 ml) was added 30% hydrogen peroxide (50 ml), and the mixture boiled under reflux for 2.5 hr. On cooling a yellow solid crystallised out, which was filtered off and dried at 10°C m.p. 179°—198°C. Recrystallisation from acetic acid gave pure 2 - methylthioxanthone - 10,10 - dioxide, m.p. 201°—203°C.

C. Preparation of 2 - carboxythioxanthone - 10,10 - dioxide

A solution of chromium dioxide (1.50 g) in water (4.0 ml) was added to 2 - methylthioxanthone - 10,10 - dioxide (1.29 g) in acetic acid (25 ml). Sulphuric acid (2.0 ml) was added and the mixture was boiled under reflux for 15 min. The mixture was cooled, and the crystallised product was filtered off, washed with water, and dried at 110°C, m.p. 276°C.

Reference Preparation 8

3 - Carboxythioxanthone - 10,10 - dioxide

A. Preparation of phenylthioterephthalonitrile

To a sodium methoxide solution, prepared by dissolving sodium (1.46 g) in dry methanol (40 ml), was added redistilled thiophenol (6.92 g), and the methanol removed on a rotary evaporator. Dimethyl sulphoxide (50 ml) was

added, and to the resulting solution nitroterephthalonitrile (10.38 g) was added. The dark brown solution was heated on the steam bath for 2 hours, then poured on to ice. The precipitated product was filtered off and dried *in vacuo* at room temperature, m.p. 106°C. Recrystallisation from ethanol gave the pure product, m.p. 111°C.

B. Preparation of phenylthioterephthalic acid

A mixture of phenylthioterephthalonitrile (6.73 g), sodium hydroxide (4.20 g), water (15 ml) and ethanol (100 ml) was boiled under reflux. As evolution of ammonia began, sodium salts began to precipitate and water was added to the reaction mixture to keep the salts in solution. After 2 hours the ethanol was allowed to distil off as more water was added to 150 ml, the solution was filtered, and poured on to ice and excess hydrochloric acid. The precipitated product was filtered off, washed with water, and dried at 110°C, m.p. 328—331°C (sublimes).

C. Preparation of thioxanthone - 3 - carboxylic acid

Phenylthioterephthalic acid (7.10 g) was heated with polyphosphoric acid (50 g) at 210—215°C for 2 hr. with occasional stirring. The dark mixture was poured into water and heated to boiling point, and the greenish product filtered off, washed with water, and recrystallised from aqueous dimethylformamide, m.p. 314°—315°C and a second crop on dilution of the half-evaporated acetic acid liquors with water, gave a m.p. 313°—314°C.

D. Preparation of 3 - carboxythioxanthone - 10,10 - dioxide

A mixture of thioxanthone - 3 - carboxylic acid (0.120 g), acetic acid (6.0 ml) and 30% hydrogen peroxide (0.12 ml) was boiled under reflux for 15 hr. filtered while hot, and allowed to cool. The product crystallised out slowly. It was filtered off and dried at 110°C, m.p. 285—287°C.

Reference Preparation 9

3 - Carboxythioxanthone - 10,10 - dioxide

To 3 - carboxythioxanthene - 10,10 - dioxide (0.72 g) (prepared as in Example 27) in pyridine (20 ml) was added 40% Triton B pyridine solution (3.5 ml), which resulted in the formation of a deep orange colour. Air was passed through the solution for 20 minutes, after which time the solution was pale green. During the reaction interruption of the air flow resulted in the development of a deep blue colour which disappeared when the flow was restarted. This did not occur when the reaction was completed. The solution was poured onto ice and excess hydrochloric acid and the pale yellow product filtered off and dried at 110°C, m.p. 257—267°C. After two recrystallisations from acetic acid the product had a m.p. of 282—284°C and its infra-red spectrum was identical with that of an authentic sample of 3 - carboxythioxanthone - 10,10 - dioxide.

Reference Preparation 10

2,6 - Dicarboxythioxanthone - 10,10 - dioxide

To stirred polyphosphoric acid (800 g) at 290°C was added diphenyl sulphone, 2,4',5 - tricarboxylic acid (56.7 g) (Bennett, Can. J. Chem., *43* 1880 (1965); and Bennett and Gauvin, J. Org. Chem., *34* 4165 (1969)) and the temperature maintained at 290°C for 1/2 hour. The mixture was cooled, and decomposed by heating with water. The black solid was filtered off and recrystallised twice from dimethyl formamide, m.p. above 400°C.

Reference Preparation 11

2,7 - Dicarboxythioxanthone - 10,10 - dioxide

A. Preparation of 2,4,4' - Trimethyldiphenyl sulphone

To a stirred mixture of anhydrous aluminium chloride (66.6 g) in m-xylene (100 ml) at 50°C was added a solution of p - toluene - sulphonyl chloride (50 g) in m-xylene (60 ml), dropwise. The temperature of the reaction mixture was allowed to rise to 80°C over 1.5 hrs. by external heating, then the mixture was cooled and poured on to ice and hydrochloric acid. The excess xylene was steam-distilled out and the oily product extracted into chloroform, washed with water and sodium bicarbonate solution, dried, and evaporated. Vacuum distillation gave 2,4,4' - trimethyldiphenyl sulphone, b.pt. 181°C at 0.5 mm.Hg.

B. Preparation of Diphenyl sulphone - 2,4,4' - tricarboxylic acid

2,4,4' - Trimethyldiphenyl sulphone (32.0 g) was heated with 35% nitric acid (200 ml) in an autoclave to 175°C over 1.5 hr. This temperature was maintained for a further 0.75 hr. After cooling the solid product was filtered off, washed with water, recrystallised from aqueous dimethylformamide, and dried at 110°C, giving diphenyl sulphone - 2,4,4' - tricarboxylic acid m.pt. 352°—353°C with decomposition.

Found:
C 51.47%; H 3.04%; S 8.98%
$C_{15}H_{10}O_8S$ requires:
C 51.44%; H 2.88%; S 9.15%

C. Preparation of 2,7 - Dicarboxythioxanthone - 10,10 - dioxide

Diphenyl sulphone - 2,4,4' - tricarboxylic acid (8.50 g) was heated with polyphosphoric acid (127 g) at 290°C for 0.5 hr. with stirring. The dark syrup was cooled and decomposed with water overnight. The dark solid product was filtered off and recrystallised twice from

dimethylformamide to give 2,7 - dicarboxythioxanthone - 10,10 - dioxide, m.pt. 372°—375°C with decomposition.

Found:
C 54.15%; H 2.47%; S 9.51%
$C_{15}H_8O_7S$ requires:
C 54.24%; H 2.43%; S 9.65%

Reference Preparation 12

3 - Methoxycarbonylthioxanthone - 10,10 - dioxide

3 - Carboxythioxanthone - 10,10 - dioxide (2.0 g), thionyl chloride (25 ml), and dimethylformamide (2 drops) were boiled together under reflux for 1 hr. The solution was evaporated to dryness, and methanol (100 ml.) added. The mixture was heated to boiling and the clear solution filtered and allowed to cool. The product, which crystalised out, was filtered off and recrystallised from methanol to give 3 - methoxycarbonyl - thioxanthone - 10,10 - dioxide, m.pt. 145°—146°C.

Found	C 59.77%; H 3.31%
$C_{15}H_{10}O_5S$ requires	C 59.60%; H 3.33%

Example 1

3 - Carboxy - 7 - ethylthioxanthone - 10,10 - dioxide

A. p-Ethylthiophenol

Chlorosulphonic acid (180 g) was added with stirring to ethylbenzene (36 g) at 10°C. This temperature was maintained by external cooling throughout the addition. When the addition was completed the mixture was poured on to ice and the product extracted into ether. The combined extracts were washed with water, dried with magnesium sulphate and evaporated.

The residual sulphonyl chloride was stirred with 25% sulphuric acid (500 ml) at 0°—5°C. while zinc dust (70 g) was added. The mixture was then heated slowly, and at 88°C an exothermic reaction began. The temperature rose until the mixture boiled gently, and the yellow, oily product detached itself from the zinc. It was steam distilled out, extracted into methylene chloride, dried, evaporated and distilled to give p-ethylthiophenol b.p. 93—98°C. at 12 mm Hg.

B. 2 - (p - Ethylphenylthio)terephthalic acid

Sodium (2.0 g) was dissolved in methanol (60 ml) and p-ethylthiophenol (10.0 g) added. The solution was evaporated to dryness and the residue dissolved in dimethylsulphoxide (60 ml). Nitroterephthalonitrile (12.32 g) was added and the mixture heated on the steam bath for 3 hr. The mixture was poured onto ice and the crude product extracted into ether. The extracts were evaporated and boiled under reflux with a solution of sodium hydroxide (9.0 g) in water (250 ml) for 16 hr. The solution was cooled and extracted with ether to remove some unchanged thiol, and the aqueous solution was poured into excess hydrochloric acid. The precipitated product was filtered off, washed with hot water, and dried at 95°C. *in vacuo*, giving 2 - (p - ethylphenylthio)terephthalic acid. A sample recrystallised from acetic acid decomposed without melting, and was microanalysed:

Found:	C 63.33%; H 4.80%
$C_{16}H_{14}O_4S$ requires:	C 63.56%; H 4.67%

C. 7 - Ethylthioxanthone - 3 - carboxylic acid

2 - (p - Ethylphenylthio)terephthalic acid (19.0 g) was heated with concentrated sulphuric acid (150 ml) at 120°C. for 1.5 hr. The solution was cooled and poured on to ice. The product was filtered off, washed with water, and recrystallised from acetic acid giving 7 - ethylthioxanthone - 3 - carboxylic acid, m.p. 261—271°C. A sample was further purified by conversion to the acid chloride. The acid (1.09 g) was boiled with thionyl chloride (*ca.* 10 ml) for 1 hr. and the excess thionyl chloride was evaporated off. The residual acid chloride was recrystallised from toluene, then hydrolysed by boiling with excess sodium hydroxide. Acidification gave the acid, which was recrystallised from acetic acid and dried at 156°C. *in vacuo*, m.p. 276—284°C, pure by thin layer chromatography.

Found:	C 67.51%; H 4.23%
$C_{16}H_{12}O_3S$ requires:	C 67.59%; H 4.25%

D. 3 - Carboxy - 7 - ethylthioxanthone - 10,10 - dioxide

7 - Ethylthioxanthone - 3 - carboxylic acid (0.25 g), 30% hydrogen peroxide (0.25 ml) and acetic acid (2.5 ml) were mixed and boiled under reflux for 4 hr. Further acetic acid was added to completely dissolve the product and the boiling solution was filtered and cooled. 3 - Carboxy - 7 - ethylthioxanthone - 10,10 - dioxide crystallised out and was filtered off and dried m.p. 300—303°C.

Found:	C 60.55%; H 3.85%
$C_{16}H_{12}O_5S$ requires:	C 60.76%; H 3.82%

Example 2

7 - tert.Butyl - 3 - carboxythioxanthone - 10,10 - dioxide

A. 2 - (p - tert.Butylphenylthio)terephthalic acid

Starting from p - tert. - butylthiophenol (8.30 g) and nitroterephthalonitrile (8.65 g), 2 - (p - tert. - butylphenylthio)terephthalic acid (5.23 g), m.p. 325—326°C, was prepared in the same way as the ethyl analogue.

Found: C 65.64%; H 5.83%
$C_{18}H_{18}O_4S$ requires: C 65.43%; H 5.49%

B. 7 - tert.Butylthioxanthone - 3 - carboxylic acid

2 - (p - tert. - butylphenylthio)terephthalic acid (5.23 g) was cyclised by heating with concentrated sulphuric acid (50 ml) on the steam bath for 10 hr. The solution was cooled and diluted with water, and the precipitated product filtered off, and recrystallised from ethanol, giving 7 - tert. - butylthioxanthone - 3 - carboxylic acid m.p. 252—257°C. A sample recrystallised from toluene followed by a further recrystallisation from acetic acid had a m.p. of 259—261°C.

Found: C 69.30%; H 5.20%
$C_{18}H_{16}O_3S$ requires: C 69.21%; H 5.16%

C. 7 - tert.Butyl - 3 - carboxythioxanthone - 10,10 - dioxide

7 - tert. - Butylthioxanthone - 3 - carboxylic acid (1.52 g) in acetic acid (15 ml) and 30% hydrogen peroxide (3.0 ml) was boiled under reflux for 2 hr. On cooling, 7 - tert.butyl - 3 - carboxythioxanthone - 10,10 - dioxide separated and was filtered off and recrystallised, once from acetic acid and once from aqueous ethanol, to give m.p. 259°—262°C.

Found: C 62.76%; H 4.69%
$C_{18}H_{16}O_5S$ requires: C 62.78% H 4.68%

Reference Preparation 13
4 - Carboxythioxanthone - 10,10 - dioxide

A. Cupric o - chlorobenzoate

o - Chlorobenzoic acid (31.3 g) was dissolved in a solution of sodium hydroxide (8.0 g) in water (250 ml) and the warmed solution filtered and treated with a solution of cupric sulphate pentahydrate (25.0 g) in water (200 ml). The precipitated blue-green solid was filtered off, washed with water, and dried to give cupric chlorobenzoate, m.p. 259°C. with decomposition.

B. Cupric complex of thiosalicylic acid

Thiosalicylic acid (30.8 g) was added to a solution of sodium hydroxide (16.0 g) in water (300 ml) and to the resulting solution was added a solution of cupric sulphate pentahydrate (50.0 g) in water (30 ml). The precipitated black complex was filtered off, washed with water and ethanol, and dried.

C. Diphenyl sulphide 2,2′ - dicarboxylic acid

A mixture of cupric o-chlorobenzoate (28.2 g), thiosalicylic acid cupric complex (32.4 g) and dimethylformamide (450 ml) was boiled under reflux for 2 hr. The dull green precipitate was filtered from the cooled mixture and allowed to stand overnight in 2*N*. hydrochloric acid (200 ml). The product was filtered off, washed with water, and heated with normal sodium hydroxide solution (400 ml). A black residue was filtered off and the filtrate acidified to precipitate diphenyl sulphide 2,2′ - dicarboxylic acid which was filtered off, washed with water and dried, m.p. 232—234°C. A sample recrystallised from acetic acid had m.p. 236°C.

Found: C 61.42%; H 3.72%
$C_{14}H_{10}O_4S$ requires: C 61.32%; H 3.68%

D. Thioxanthone - 4 - carboxylic acid

Diphenyl sulphide 2,2′ - dicarboxylic acid (19.0 g) was heated on a steam bath with concentrated sulphuric acid (150 ml) for 1 hr., and the dark solution cooled and poured into water. The yellow precipitate was filtered off, washed well with water and dried, given thioxanthone - 4 - carboxylic acid. A sample recrystallised from dimethylformamide, then acetic acid, had m.p. 353°C (with sublimation).

Found: C 65.47%; H 3.14%
$C_{14}H_8O_3$ requires: C 65.74%; H 3.28%

E. 4 - Carboxythioxanthone - 10,10 - dioxide

Thioxanthone - 4 - carboxylic acid (5.0 g), acetic acid (100 ml) and 30% hydrogen peroxide (5.0 ml) were boiled under reflux for 1 hr. On cooling, 4 - carboxythioxanthone - 10,10 - dioxide crystallised out and was filtered off and dried, m.p. 237°C.

Found: C 58.14%; H 2.95%
$C_{14}H_8O_6$ requires: C 58.34%; H 2.80%

Reference Preparation 14
3 - Carboxythianthrene - 5,5 - dioxide

A. 4 - Chloro - 3 - mercaptobenzoic acid

3 - Amino - 4 - chlorobenzoic acid (34.3 g) was added to 5*N* hydrochloric acid (120 ml) and cooled to 0°C. To the stirred suspension was added a solution of sodium nitrate (14.5 g) in water (35 ml) over 30 min. with the temperature maintained at 0° to 5°C. The yellow diazonium solution, containing some suspended solid was added to a solution of potassium ethyl xanthate (37.5 g) in water (60 ml), containing 0.2 g nickel chloride, at 45—50°C. Nitrogen evolution occurred and the yellow solid which precipitated at first decomposed to a red oil which then solidified. When the addition was complete, the mixture was heated to 70°C., cooled, and the red solid filtered off and washed with water. It was then boiled with a solution of potassium hydroxide (60 g) in water (300 ml) for 2 hr., cooled, filtered and acidified with excess hydrochloric acid. Thin-layer chromatography indicated the presence of 2 components in

the precipitated creamy solid. Recrystallisation from acetic acid yielded a by-product, m.p. 240°—290°C., and dilution of the recrystalisation liquors gave a solid which was recrystallised from aqueous ethanol yielding mainly 4 - chloro - 3 - mercaptobenzoic acid, m.p. 209°—211°C.

B. 4 - Chloro - 3 - (o - nitrophenylthio)-benzoic acid

Sodium (2.93 g) was dissolved in dry methanol (100 ml), 4 - chloro - 3 - mercaptobenzoic acid (12.0 g) added, and the solution evaporated to dryness. The residue was dissolved in dimethylsulphoxide (130 ml) and o-chloronitrobenzene (10.0 g) added. The mixture was heated on the steam bath for 30 min., poured into water, and extracted with chloroform (2×75 ml). The aqueous solution was acidified with hydrochloric acid and the precipitated 4 - chloro - 3 - (o - nitrophenylthio) - benzoic acid filtered off, washed with water, and recrystallised from acetic acid, m.p. 261°—262°C.

C. 4 - Chloro - 3 - (o - nitrophenylsulphonyl)benzoic acid

4 - Chloro - 3 (o - nitrophenylthio)benzoic acid (13.1 g), acetic acid (250 ml) and 30% hydrogen peroxide (17.5 ml) were boiled together under reflux for 1 hr. Two further (17.5 ml) portions of hydrogen peroxide were added, refluxing 1 hr. after each addition, and the reaction mixture then cooled, diluted with water, and 4 - chloro - 3 - (o - nitrophenylsulphonyl)benzoic acid filtered off, washed with water and dried, m.p. 242°—245°C. A sample recrystallised from methanol had m.p. 244°—246°C.

D. 3 - (o - Aminophenylsulphonyl) - 4 - chlorobenzoic acid

A mixture of 4 - chloro - 3 - (o - nitrophenylsulphonyl)benzoic acid (1.71 g), stannous chloride (3.12 g), concentrated hydrochloric acid (6.6 ml) and acetic acid (25 ml) was heated on the steam bath for 30 min., cooled, and diluted with water. 3 - (o - Aminophenylsulphonyl) - 4 - chlorobenzoic acid was filtered off, washed with water and dried, m.p. 235°—238°C, providing on recrystallisation from acetic acid, m.p. 246°—248°C.

E. 3 - Carboxythianthrene - 5,5 - dioxide

3 - (o - Aminophenylsulphonyl) - 4 - chlorobenzoic acid (6.00 g) was stirred with concentrated hydrochloric acid (8.0 ml) and water (12.0 ml) and treated at 0°—5°C. with a solution of sodium nitrite (1.50 g) in water (30 ml) over 30 min. After a further 15 min. stirring the suspension was pipetted into a solution of potassium ethyl xanthate (10.2 g) and sodium hydroxide (1.60 g) in water (50 ml) of 45°—50°C. Vigorous nitrogen evolution took place. After the addition was complete the now clear solution was heated to boiling and further sodium hydroxide (3.20 g) was added. Boiling was continued for a further 20 min., and the solution then cooled, filtered and acidified with hydrochloric acid. The solid precipitated acid was filtered off, washed with water, and recrystallised from acetic acid to give 3-carboxythianthrene - 5,5 - dioxide, m.p. 297°—304°C; on further recrystallisation from ethanol it had m.p. 302°—305°C.

Found: C 53.35%; H 2.94%
$C_{13}H_8O_4S_2$ requires: C 53.43%; H 2.76%

Example 3

2 - Carboxy - 8 - methylphenoxanthiin - 10,10 - dioxide

A. 4,4′ - Dimethyldiphenyl ether

p-Bromotoluene (51 g), p-cresol (33 g) and potassium hydroxide (18.5 g) were mechanically stirred on a steam bath for 30 min., then heated at 190°C. for 1 hr. Copper bronze (2.0 g) was added and the heating continued for a further 1 hr. at 190°C., then 220° to 230°C. for 2.5 hr. After cooling, the residue was extracted into chloroform, filtered, and the extract washed with water, dried, evaporated and crystallised from ethanol to yield 4,4′ - dimethyldiphenyl ether, m.p. 49—50°C.

B. 2,8 - Dimethylphenoxathiin

4,4′ - Dimethyldiphenyl ether (28.0 g), sulphur (4.40 g) and aluminium chloride were stirred and heated together at 75—80°C. for 1 hr. and 100°C for 4 hr. The mixture was cooled and poured into hydrochloric acid. The oily solid product was separated, triturated with methanol and filtered off, and the product, 2,8 - dimethylphenoxathiin, recrystallised from methanol, m.p. 69—70°C.

C. 2,8 - Dimethylphenoxathiin - 10,10 - dioxide

2,8 - Dimethylphenoxathiin (5.90 g) was dissolved in boiling acetic acid (30 ml) and 30% hydrogen peroxide (10.0 ml) was added dropwise. After 2 hours boiling under reflux the resulting solution was filtered while boiling, and on cooling 2,8 - dimethylphenoxathiin - 10,10 - dioxide crystallized out and was filtered off and dried, m.p. 175—176°.

D. 2 - Carboxy - 8 - methylphenoxathiin - 10,10 - dioxide

2,8 - Dimethylphenoxathiin - 10,10 - dioxide (5.30 g) was dissolved in boiling acetic acid (100 ml) and chromium trioxide (5.70 g) in acetic acid (50 ml) added. The solution was boiled under reflux for 6 hr. On cooling starting material (2.38 g), m.p. 177—178°C. crystallised out and was filtered off, and dilu-

tion with water yielded further solid material (2.00 g) which was warmed with 5% sodium bicarbonate solution and filtered, giving 1.35 g starting material m.p. 170—174°C. Acidification of the filtrate with hydrochloric acid gave 2 - carboxy - 8 - methylphenoxathin - 10,10 - dioxide, which was filtered off and washed with water, m.p. 274—276°C.

Found: C 57.69%; H 3.35%
$C_{14}H_{10}O_5S$ requires: C 57.94%; H 3.47%

Example 4
3 - Carboxy - 7 - chlorothioxanthone - 10,10 - dioxide

A. p - Chlorophenylthioterephthalonitrile

Sodium (1.15 g) was dissolved in dry methanol (35 ml), and p - chlorothiophenol (7.23 g) was added. The solution was evaporated and dimethylsulphoxide (40 ml) added to the residue, followed by nitroterephthalonitrile (8.65 g). The solution was heated on a steam bath for 30 mins., poured into cold water, and the precipitated p - chlorophenylthioterephthalonitrile filtered off, washed with water, and dried, m.p. 162°—165°C. A sample recrystallised from *iso*propanol had m.p. 167°—168°C.

B. p - Chlorophenylthioterephathalic acid

p - Chlorophenylthioterephthalonitrile (8.0 g) was boiled under reflux with sodium hydroxide (4.55 g) in water (150 ml) for 16 hr. Filtration of the hot solution gave the diamide, m.p. 308°—310°C., and acidification of the filtrate with hydrochloric acid yielded p - chlorophenylthioterephthalic acid, m.p. 346°—347°C. A sample recrystallised from acetic acid had m.p. 353°—354°C.

C. p - Chlorophenylsulphonylterephthalic acid

p - Chlorophenylthioterephthalic acid (2.0 g), acetic acid (20 ml) and 30% hydrogen peroxide (2.0 ml) were boiled together under reflux for 30 min. Further peroxide (2.0 ml) was added and boiling continued for a further 30 min. The solution was partially evaporated, diluted with water, and the precipitated p-chlorophenylsulphonylterephthalic acid filtered off and recrystallised from aqueous acetic acid m.p. 270°—272°C.

D. 3 - Carboxy - 7 - Chlorothioxanthone - 10,10 - dioxide

p - Chlorophenylsulphonylterephthalic acid (5.0 g) was dissolved in concentrated sulphuric acid (50 ml) and heated at 240°C. for 2 hr. The solution was cooled, poured on to ice, and the precipitated 3 - carboxy - 7 - chlorothioxanthone - 10,10 - dioxide filtered off, washed with water, and recrystallised from acetic acid, m.p. 352°—355°C.

Found: C 52.06%; H 2.16%
$C_{14}H_7ClO_5S$ requires: C 52.10%; H 2.19%

Example 5
3 - Carboxy - 7 - methoxythioxanthone - 10,10 - dioxide

A. p - Methoxyphenylthioterephthalonitrile

Sodium (4.66 g) was dissolved in methanol (120 ml) and p-methoxythiophenol (28.3 g, prepared by the method used for p-ethylthiophenol) was added. The solution was evaporated to dryness and the residue dissolved in dimethylsulphoxide (200 ml). Nitroterephthalonitrile (34.9 g) was added, and the resulting solution heated on the steam-bath for 1 hr. On diluting the cooled solution with water, p-methoxyphenylthioterephthalonitrile crystallised out and was filtered off and dried. A sample recrystallised from ethanol had m.p. 126°—127°C.

B. p - Methoxyphenylthioterephthalic acid

p - Methoxyphenylthioterephthalonitrile (1.60 g), sodium hydroxide (0.91 g) and water (30 ml) were boiled together under reflux for 8 hr. A solid residue was filtered from the reaction mixture and the filtrate acidified with hydrochloric acid. p - Methoxyphenylthioterephthalic acid was filtered off, washed with water and dried. A sample recrystallised from acetic acid had m.p. 326°C.

C. 7 - Methoxythioxanthone - 3 - carboxylic acid

p - Methoxyphenylthioterephthalic acid (13.4 g) was heated with polyphosphoric acid (260 g) at 120°C. for 2 hr., then at 140°C for 4 hr. The reaction mixture was decomposed by warming with water and the solid product was filtered off and washed well with water. Recrystallisation from acetic acid gave impure 7 - methoxythioxanthone - 3 - carboxylic acid, m.p. >360°C.

D. 3 - Carboxy - 7 - methoxythioxanthone - 10,10 - dioxide

7 - Methoxythioxanthone - 3 - carboxylic acid (1.50 g), acetic acid (25 ml) and 30% hydrogen peroxide (1.0 ml) were boiled together under reflux for 2 hr. Some solid remained undissolved. The mixture was cooled and filtered, and the residue recrystallised first from acetic acid, then from dimethylformamide to give 3 - carboxy - 7 - methoxythioxanthone - 10.10 - dioxide, m.p. 324°—327°C.

Found: C 56.33%; H 3.15%
$C_{15}H_{10}O_6S$ requires: C 56.61%; H 3.17%

Reference Preparation 15
3 - Carboxydibenzothiophene - 5,5 - dioxide

A. Preparation of 3 - nitrodibenzothiophene - 5,5 - dioxide

To a mixture of acetic acid (77 ml) and sulphuric acid (77 ml) was added dibenzothio-

phene - 5,5 - dioxide (35.0 g), and the mixture cooled to 4°C. Addition of a total of 197 g (131 ml) fuming nitric acid was begun, but in a short time the resulting paste became too thick to stir efficiently, and a further 77 ml. acetic acid was added. Local heating due to inefficient stirring was observed to occur, but the temperature of the reaction mixture was maintained at 4°C as far as was possible. When the addition was complete (ca. 20 min.), the mixture was stirred at 4°C for a further 30 min., and then poured into water. The crude nitrocompound was filtered off and recrystallised from dimethylformamide, m.p. 259°C.

B. Preparation of 3 - aminodibenzothiophene - 5,5 - dioxide hydrochloride

A mixture of 3 - nitrodibenzothiophene - 5,5 - dioxide (30.0 g), granulated tin (75 g) concentrated hydrochloric acid (425 ml) and water (750 ml) was boiled under reflux until all of the yellow nitro-compound was dissolved (2.5 hr.). The boiling solution was filtered through a sintered glass funnel, leaving undissolved tin (ca. 24 g), and the crystalline hydrochloride, which separated from the solution on cooling, was filtered off and dried at room temperature *in vacuo*, m.p. 235°C.

C. Preparation of 3 - carboxydibenzothiophene - 5,5 - dioxide

To a vigorously stirred suspension of 3 - aminodibenzothiophene - 5,5 - dioxide hydrochloride (27.35 g) in concentrated hydrochloric acid (40 ml) to which ice (150 g) had been added, was added at 0°C a solution of sodium nitrite (7.2 g) in water over 15 min. After the addition was complete, the mixture was stirred at 5°C for 10 min., and the solid material filtered off and washed with water. The solid was added to a solution of cuprous cyanide, prepared freshly from cupric sulphate pentahydrate (17.0 g) and potassium cyanide (8.84 g) in water (25 ml). The mixture was heated steadily to boiling over 20 min., cooled, and filtered. The solid residue was extracted with boiling ethanol (2×1 litre). Insoluble material was discarded. The ethanol - soluble material, after evaporation of the solvent was boiled for 6 hrs. with potassium hydroxide (10 g) in water (150 ml) and ethanol (150 ml). The ethanol was evaporated off and water added, and some unchanged amine filtered off. The filtrate was acidified with hydrochloric acid and the precipitated acid filtered off and recrystallised from acetic acid, m.p. 312°C.

Reference Preparation 16

3 - Carboxythioxanthene - 10,10 - dioxide

3 - Carboxythioxanthone - 10,10 - dioxide (prepared as in Reference Preparation 4) (5.0 g), zinc wool (10.0 g) and mercuric acetate (0.2 g) in acetic acid (100 ml) were brought to the boil and concentrated hydrochloric acid (10 ml) was added. Vigorous evolution of hydrogen chloride occurred at first. After 2 hr., further hydrochloric acid (7 ml), was added and the mixture boiled under reflux for further 4 hr. It was then filtered while hot and poured on to ice and water. The precipitated product was filtered off and dried at 80°C *in vacuo*, m.p. 229—248°C. Two recrystallisations from methanol gave the product m.p. 254°C.

Example 6

3 - Carboxy - 7 - methylthioxanthone - 10,10 - dioxide

A. Preparation of 2 - (p - tolylthio)terephthalonitrile

To a solution of sodium methoxide (made from sodium (2.18 g) in methanol (50 ml) was added p-toluene thiol (11.8 g). The solution was evaporated to dryness and the residual sodium salt dissolved in dry dimethylsulphoxide (150 ml). Nitroterephthalonitrile (15.56 g) was added and the resulting dark solution was heated on the steam bath for 30 min., then poured into water. The precipitated product was filtered off, washed with water and dried at room temperature *in vacuo*, m.p. 155°C.

B. Preparation of 2 - (p - tolylthio)terephthalic acid.

The dinitrile (14.5 g) was dissolved in ethanol (100 ml) and sodium hydroxide (9.5 g) in water (100 ml) was added. The mixture was boiled under reflux for 30 min., the ethanol distilled off and the residual solution filtered and boiled for a further 7-1/2 hours. It was then poured onto excess hydrochloric acid and ice and the precipitated acid filtered off, washed with water, and dried at 100°C, m.p. 326°C (decomposes).

C. Preparation of 7 - methylthioxanthanethone - 3 - carboxylic acid

2 - (p - Tolythio)terephthalic acid (13.5 g) was stirred and heated with polyphosphoric acid (330 g) at 100°C for 3 hours. The mixture was decomposed with water and the ochre-coloured acid filtered off and recrystallised from acetic acid, m.p. 321—323°C.

D. Preparation of 3 - carboxy - 7 - methylthioxanthone - 10,10 - dioxide

7 - Methylthioxanthone - 3 - carboxylic acid (4.0 g) was dissolved in acetic acid (400 ml) and 30% hydrogen peroxide (15 ml) was added. The mixture was boiled under reflux for 2 hours and cooled. The product, which crystallised out, was filtered off and dried at 110°C, m.p. 357°C (decomposes).

Example 7

3 - Carbamoyl - 7 - Methylthioxanthone - 10,10 - dioxide

3 - Carboxy - 7 - methylthioxanthone -

10,10 - dioxide (0.99 g) was boiled with thionyl chloride (10 ml) containing 1 drop dimethyl formamide for 2 hours. The solution was evaporated to dryness and the solid acid chloride residue added to 15% ammonia solution (30 ml) with stirring. After 1 hour the amide was filtered off, washed with water, and dried at 100°C, m.p. 305°C (decomposes).

Example 8

3 - Carboxythioxanthone - 10,10 - dioxide sodium salt

3 - Carboxythioxanthone - 10,10 - dioxide (2.88 g: 10 mmole) was dissolved in *N* sodium hydroxide (10 ml) to give a dark-coloured solution, which was then evaporated to dryness under reduced pressure.

The solid residue was recrystallised from aqueous ethanol and the product dried at 100°C. A second crop was obtained from the recrystallisation liquors on standing. This was filtered off, and dried at 100°C to yield the product, 3 - carboxythioxanthone - 10,10 - dioxide sodium salt (hydrated). Further drying at 156°C./20 m.m. Hg gave the anhydrous compound having the infra red spectrum shown in the accompanying drawing when dispersed in a potassium bromide disc (Unicam SP 200 (Unicam Instruments Ltd., Cambridge).

Example 9

3 - Carboxythioxanthone - 10,10 - dioxide ethanolamine salt

To 3 - carboxythioxanthone - 10,10 - dioxide (2.88 g) was added a solution of ethanolamine (0.61 g) in water (10 ml). The solution was filtered and evaporated to dryness, leaving a residue of 3 - carboxythioxanthone - 10,10 - dioxide ethanolamine salt m.p. 195°C. with decomposition.

Found:
C 54.98%; H 4.33%; N 3.93%
$C_{16}H_{15}NO_6S$ requires:
C 55.01%; H 4.33%; N 4.01%

Example 10

3 - Carboxy - 7 - nitrothioxanthone - 10,10 - dioxide

A. 7 - Nitrothioxanthone - 3 - carboxylic acid

Sodium 4 - nitrothiophenoxide (from 1.55 g of 4 - nitrothiophenol was heated with 2,5 - dicyanonitrobenzene (1.73 g) in dimethyl - sulphoxide (30 ml) at 100°C for 1 hr. After standing overnight the solution was diluted with water and dilute sodium carbonate and the precipitate of 2,5 - dicyano - 4′ - nitrodiphenylsulphide (2.65 g) collected by filtration. This compound had m.p. 181°C. when recrystallised. To hydrolyse the dinitrile, it was refluxed with a mixture of 60% w/w sulphuric acid (70 ml) and glacial acetic acid (45 ml) for 3.5 hr. and the resulting *p*-nitrothiophenoxyterephthalic acid filtered off. This was cyclised by heating with an excess of phosphorus oxychloride for 24 hr., removing the solvent under reduced pressure, and again heating for 21 hr. at 135°C. with an excess of polyphosphoric acid. On addition to warm water 2 - nitrothioxanthone - 6 - carboxylic acid was precipitated; from a mixture of dimethylformamide, dimethylsulphoxide and ethanol, the acid formed crystals which sublimed but did not melt up to 410°C.

B. 3 - Carboxy - 7 - nitrothioxanthone - 10,10 - dioxide

7 - Nitrothioxanthone - 3 - carboxylic acid (0.65 g) acetic acid (125 ml) and 30% hydrogen peroxide (3.0 ml) were boiled together under reflux for 18 hr. The solution was filtered off and 3 - carboxy - 7 - nitrothioxanthone - 10,10 - dioxide crystallised out slowly and was filtered off and dried at 156°C. *in vacuo*, m.p. >360°C.

Found:
C 50.49%; H 2.30%; N 4.05%
$C_{14}H_7NO_7S$ requires:
C 50.46%; H 2.12%; N 4.20%

Reference Preparation 17

2,5 - Dicarboxythioxanthone - 10,10 -dioxide

A. Thioxanthone - 2,5 - dicarboxylic acid

Sodium 4 - cyanothiophenoxide (from 2.7 g of 4 - cyanothiophenol) was heated with 2,6 - dicyanonitrobenzene (3.5 g) in dimethylsulphoxide (20 ml) at 110°C. overnight. On dilution with water, 2,4′,6 - tricyanodiphenylsulphide, m.p. 172—173°C. was obtained. This was hydrolysed by refluxing for 5 hr. in 60% sulphuric acid (40 ml) and glacial acetic acid (25 ml); a solid precipitate of diphenylsulphide - 2,4′,6 - tricarboxylic acid being formed. This was cyclised in concentrated sulphuric acid at 90—100°C: after 4 hr. heating the solution was poured onto ice. The resulting thioxanthone - 2,5 - dicarboxylic acid, on crystallisation from dimethylformamide-ethanol, formed crystals, m.p. *ca.* 400°C., which contained one quarter of a molecule of dimethyl formamide of solvation.

B. 2,5 - Dicarboxythioxanthone - 10,10 - dioxide

Thioxanthone - 2,5 - dicarboxylic acid (0.52 g), acetic acid (25 ml) and 30% hydrogen peroxide (1.5 ml) were boiled together under reflux for 2.5 hr. Further acetic acid (*ca.* 100 ml) was added to dissolve all of the product, the solution was filtered while boiling, and on cooling 2,5 - dicarboxythioxanthone - 10,10 - dioxide crystallised out and was filtered off and dried, m.p. 350—351°C.

Found: C 53.94%; H 2.46%
$C_{15}H_8O_7S$ requires: C 54.22%; H 2.43%

Reference Preparation 18
1 - Carboxythioxanthone - 10,10 - dioxide

A. Thioxanthone - 1 - carboxylic acid

Sodium thiophenoxide (from 3.3 g of thiophenol) was heated at 100°C. in dimethylsulphoxide (30 ml) with 2,3 - dicyanonitrobenzene (5.2 g) for 4.5 hr. On dilution with water, 3 - thiophenoxyphthalodinitrile, m.p. 116—117°C., was obtained. This was refluxed with 60% sulphuric acid (105 ml) and acetic acid (66 ml) for 5.5 hr. to give the corresponding phthalic acid, which was then cyclized by heating with an excess of polyphosphoric acid for 72 hr. at 135—145°C. Addition to warm water gave a precipitate of thioxanthone - 1 - carboxylic acid which yielded crystals, m.p. 264—265°C. from a mixture of dimethylformamide and aqueous ethanol.

B. 1 - Carboxythioxanthone - 10,10 - dioxide

Thioxanthone - 1 - carboxylic acid (0.60 g), acetic acid (15 ml) and 30% hydrogen peroxide solution (0.60 ml) were boiled under reflux together for 8 hr., during which time a further two (0.60 ml) portions of peroxide were added at intervals. The boiling solution was filtered, and on cooling 1 - carboxythioxanthone - 10,10 - dioxide crystallised out and was filtered off and dried, m.p. 269—271°C.

Found: C 58.08%; H 2.84%
$C_{14}H_8O_5S$ requires: C 58.33%; H 2.80%

Reference Preparation 19
3 - Carboxythianthrene - 5,5,10 - trioxide

3 - Carboxythianthrene - 5,5 - dioxide (60 mg), acetic acid (2.0 ml) and 30% hydrogen peroxide (0.10 ml) were boiled under reflux for 10 mins., filtered and allowed to stand overnight at 0°C. 3 - Carboxythianthrene - 5,5,10 - trioxide crystallised out, was filtered off and dried at 156°C at 2 mm. Hg., m.p. 340—343°C.

Analysis:
Found: C 50.38%; H 2.75%
Required for $C_{13}H_8O_5S_2$:
C 50.66%; H 2.62%

Reference Preparation 20
4,5 - Dicarboxythioxanthone - 10,10 - dioxide

A. Thioxanthone - 4,5 - dicarboxylic acid

Methyl thiosalicylate (2.84 g) was treated with a molar solution of sodium methoxide in methanol (16.9 ml) and the solvent removed under reduced pressure (final temperature 100°C) to give the dry sodium salt of the ester. This was then heated with 2,6 - dicyanonitrobenzene (2.9 g) in dry methyl sulphoxide (15 ml) for 70 hours at 105°C. After addition of water and dilute aqueous sodium carbonate, the resulting precipitate was collected and crystallised from ethanol to give 2,6 - dicyano - 2' - methoxycarbonyl diphenyl sulphide, m.p. 150°C (1.35 g). Hydrolysis of this to the corresponding acid was achieved by refluxing for 7 hours with a mixture of acetic acid (18 ml) and 60% w/w aqueous sulphuric acid; 2,2',6 - tricarboxydiphenyl sulphide, obtained from the hydrolysis medium by filtration, and washed with water, was dried and then cyclised by heating in concentrated sulphuric acid for 2-1/2 hours at 95—100°C. The yellow precipitate formed on addition to water was dried and crystallised from a mixture of dimethylformamide and ethanol. The crystals of thioxanthone - 4,5 - dicarboxylic acid so obtained melted at *ca.* 405°C with sublimation.

B. 4,5 - Dicarboxylthioxanthone - 10,10 - dioxide

Thioxanthone - 4,5 - dicarboxylic acid (0.41 g) was boiled with acetic acid (30 ml) and 30% hydrogen peroxide (0.4 ml) for 5 hr, during which time a further 0.5 ml. hydrogen peroxide was added in small portions. The solution was filtered while boiling, and on cooling 4,5 - dicarboxythioxanthone - 10,10 - dioxide crystallised out, m.p. 375°C with decompositon.

Example A
Inhalation Aerosol

3 - Carboxythioxanthone - 10,10 - dioxide (0.5—7.0 μm powder	200 mg
Sorbitan Trioleate	100 mg
Saccharin Sodium (0.5—7.0 μm powder)	5 mg
Menthol	2 mg
Trichlorofluoromethane	4.5 g
Dichlorodifluoromethane to	10.0ml

The Sorbitan Trioleate and Menthol were dissolved in the Trichlorofluoromethane. The Saccharin Sodium and Carboxylic Acid were dispersed in the mixture which was then transferred to a suitable aerosol canister and the Dichlorofluoromethane injected through the valve system. This composition provides 2 mg. of Acid in each 100 mμ dose.

Example B
Tablet

3 - Carboxythioxanthone - 10,10 - dioxide	500 mg
Maize Starch	100 mg
Microcrystalline Cellulose	75 mg
Magnesium Stearate	10 mg

Granulated with Polyvinylpyrroidone 100 w/v in 50% w/v aqueous ethanol.

The Carboxylic Acid, Maize Starch and Microcrystalline Cellulose were mixed together, and granulated with the alcoholic polyvinylpyrrolidone. The resulting granules were dried, and compressed to produce tab-

lets, each tablet, having a weight of approximately 690 mg.

Example C
Foaming Non-aqueous Aerosol for Topical Use

3 - Carboxythioxanthone - 10,10 - dioxide (fine powder)	5.0 g
Polyethylene Glycol 400	80.0 g
Propylene Glycol Monostearate, self-emulsifying	5.0 g
Dichlorodifluoromethane (Propellant 12)	4.0 g
Dichlorotetrafluoroethanethane (Propellent 114)	6.0 g

The Carboxylic acid was dispersed in a mixture of the Proplene Glycol Monostearate, self-emulsifying and the Propylene Glycol. An aerosol canister, was filled with the mixture, the valve sealed on and pressurisation effected by injecting the propellents through the valve.

Example D
Foaming Aqueous Aersol for Topical Use
Part A

3 - Carboxythioxanthone - 10,10 - dioxide sodium salt	2.2 g
Triethanolamine	3.2 g
Glycerin	4.7 g
Polyvinylpyrrolidone	0.3 g
Purified water B.P.	81.0 g

Part B

Myristic Acid	1.3 g
Stearic Acid	5.3 g
Cetyl Alcohol	0.5 g
Lanolin	0.2 g
Isopropyl Myristate	1.3 g

Propellents

Dichlorodifluoremethane	4.0 g
Dichlorotetrafluoroethane	6.0 g

The ingredients of Part B were melted together at 70°C. A solution of the ingredients of Part A in the Purified Water at the same temperature, was added to the melted ingredients of Part B. The resulting emulsion was homogenised and cooled to room temperature. The emulsion was filled into an aerosol canister, the valve crimped on and pressurisation effected by injecting the mixed propellents through the valve.

Example E
Nasal Drops

3 - Carboxythioxanthone - 10,10 - dioxide sodium salt	5.0 g
Chlorbutol	0.5 g
Purified Water B.P. to	100.0 ml

The ingredients were dissolved in 95 ml. Purified water at room temperature. The resulting mixture was made up to 100 mls with Purified Water and clarified by filtration.

Example F
Eye Drops

3 - Carboxythioxanthone - 10,10 - dioxide sodium salt	5.0 g
Methyl Hydroxybenzoate	0.10 g
Propyl Hydroxybenzoate	0.04 g
Purified Water B.P. to	100.00 ml

The Methyl and Propyl Hydroxybenzoates were dissolved in 70 ml. Purified Water at 75°C and the resulting solution then allowed to cool. The sodium carboxylate salt was added next and the solution made up to 100 ml. with purified water. The solution was sterilised by filtration through a membrane filter 0.22μm pore size and packed aseptically into suitable sterile containers.

Example G
Injection Solution

3 - Carboxythioxanthone - 10,10 - dioxide sodium salt	50.0 mg
Water for Injections B.P. to	1.0 ml

The sodium carboxylate salt was dissolved in half of the Water and then made up to volume and sterilised by filtration. The resulting solution was distributed into ampoules under aseptic conditions.

Example H
Suppositories

3 - Carboxythioxanthone - 10,10 - dioxide	200 mg
Suppository Base	1.8 g

The carboxylic acid in fine powder form was dispersed into a little of the molten suppository Base at 50°C. The dispersion was incorporated into the bulk of the base at the same temperature, allowed to cool at 42—45°C. and poured into suitable 2 g suppository moulds and allowed to set at 15—20°C. Suppository Bases were Massa Esterinum C and Witten H Suppository Compound.

Example I
Dispersible Tablet

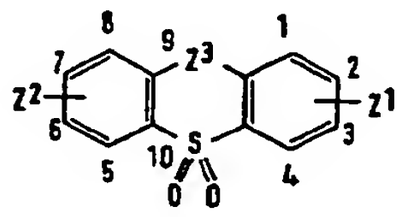
	Per tablet
3 - carboxythioxanthone - 10,10 - dioxide	200.00 mg
Maize Starch	40.00 mg
Primojel (Trade name: sodium starch glycollate (125 μm powder)	50.00 mg
Dicalcium Phosphate Dihydrate	50.00 mg
Sodium Carboxymethyl Cellulose	2.00 mg
Diocyl Sodium Sulphosuccinate	0.25 mg
Sodium Saccharin	5.00 mg
Microcrystalline Cellulose	50.00 mg
Magnesium Stearate	3.00 mg
	400.25 mg

The carboxylic acid, half of the Maize Starch, the Primojel and Dicalcium Phos-

phate were mixed together and then granulated with a solution of Sodium Carboxymethyl Cellulose, Dioctyl Sodium Sulphosuccinate and Sodium Saccharin in a suitable volume of 50% Ethyl Alcohol. The granules were dried, the remaining Maize Starch, the Microcrystalline Cellulose and the Magnesium Stearate were blended in and the resulting mixture compressed into tablets each having a weight of 400.25 mg.

WHAT WE CLAIM IS:—

1. A pharmaceutical composition comprising a tricyclic compound of formula (I)



(I)

wherein Z^1 is a substituent in the 1-, 2-, 3-, or 4-position and is carboxyl

Z^2 is hydrogen or a substituent in the 5-, 6-, 7-, or 8-position selected from carboxyl, alkylsulphonyl, alkylsulphinyl, alkylthio, amino, alkanoylamino, nitro cyano, halogen, alkanoyl, alkyl or alkoxy wherein the "alkyl" moiety of each of the alkanoyl, alkyl, alkoxy, alkylthio, alkanoylamino, alkylsulphinyl and alkylsulphonyl groups has 1 to 6 carbon atoms; and

Z^3 represents a bond or is carbonyl, oxygen, sulphur, sulphoxide or methylene;

or a pharmaceutically acceptable salt thereof; or when at least one of Z^1 and Z^2 is a carboxyl group, an ester or amide thereof, provided that when Z^3 is carbonyl and Z^1 is in the 2-position then Z^2, when a substituent in the 5-, 6-, or 7-position, is other than halogen, alkanoyl, alkyl, alkoxy, alkylthio, alkylsulphinyl and alkylsulphonyl,

in association with a pharmaceutically acceptable carrier therefor.

2. A pharmaceutical composition comprising a tricyclic compound of formula (I) according to claim 1

wherein Z^3 is carbonyl, Z^1 is a substituent in the 3-position and is carboxyl and Z^2 is hydrogen or a substituent in the 5-, 6-, 7- or 8-position selected from carboxyl, nitro, chloro, bromo, and alkyl having 1 to 6 carbon atoms; or a pharmaceutically acceptable salt thereof; in association with a pharmaceutically acceptable carrier therefor.

3. A pharmaceutical composition according to claim 1 wherein the tricyclic compound of formula (I) is selected from 3 - carboxythioxanthone - 10,10 - dioxide and its salts with pharmaceutically acceptable cations.

4. A pharmaceutical composition comprising a tricyclic compound of formula (I) according to claim 1 wherein Z^1 is a substituent in the 3-position and is a carboxyl group, a pharmaceutically acceptable carboxylate salt group, an alkyl carboxylate group wherein the alkyl moiety has 1 to 6 carbon atoms, or a carboxamide group optionally *N*-substituted by alkyl having 1 to 6 carbon atoms;

Z^2 is hydrogen or a substituent in the 5-, 6-, 7-, or 8-position selected from the values of the group Z^1 as defined above or is an alkylsulphonyl group, an alkylsulphinyl group, an alkylthio group, an amino group, an alkanoylamino group, a nitro group, a cyano group, a halogen atom, an alkanoyl group, an alkyl group or an alkoxy group wherein the "alkyl" moiety of each of the alkanoyl, alkyl, alkoxy, alkylthio, alkanoylamino, alkylsulphinyl and alkylsulphonyl groups has 1 to 6 carbon atoms; and

Z^3 represents a bond or is carbonyl, oxygen, sulphur, sulphoxide or methylene; in association with a pharmaceutically acceptable carrier therefor.

5. A pharmaceutical composition comprising a tricyclic compound of formula (I) according to claim 1, wherein Z^2 is hydrogen, Z^3 is as defined in Claim 1, and Z^1 is in the 3-position and is selected from a carboxyl group, a pharmaceutically acceptable carboxylate salt group, an alkyl carboxylate group having 1 to 6 carbon atoms in the alkyl moiety, and a carboxamide group optionally *N*-substituted by an alkyl group having 1 to 6 carbon atoms; in association with a pharmaceutically acceptable carrier therefor.

6. A pharmaceutical composition as claimed in claim 5 wherein, in the tricyclic compound of formula (I), Z^3 is oxygen or carbonyl.

7. A pharmaceutical composition comprising a tricyclic compound of formula (I) according to claim 1 wherein Z^3 is as defined in Claim 1, Z^1 is in the 3-position, Z^2 is in the 7-position and Z^1 and Z^2 are the same or different and each is selected from a carboxyl group, a pharmaceutically acceptable carboxylate salt group, an alkyl carboxylate group having 1 to 6 carbon atoms in the alkyl moiety, and a carboxamide group optionally *N*-substituted by an alkyl group having 1 to 6 carbon atoms; in association with a pharmaceutically acceptable carrier therefor.

8. A composition as claimed in any of claims 1, 4, 5 and 7 wherein Z^1 is a carboxyl or a pharmaceutically acceptable carboxylate salt group.

9. A composition as claimed in any of claims 1, 4, 5 and 7 wherein Z^3 is carbonyl, oxygen or sulphur.

10. A pharmaceutical composition comprising 2 - carboxyphenoxathiin - 10,10 - dioxide or a pharmaceutically acceptable salt thereof in association with a pharmaceutically acceptable carrier therefor.

11. A pharmaceutical composition comprising 2,6 - dicarboxythioxanthone - 10,10 - dioxide or a pharmaceutically acceptable salt

thereof in association with a pharmaceutically acceptable carrier therefor.

12. A pharmaceutical composition comprising 7 - methyl - 3 - carboxythioxanthone - 10,10 - dioxide, or a pharmaceutically acceptable salt thereof; in association with a pharmaceutically acceptable carrier therefor.

13. A pharmaceutical composition as claimed in any of claims 1 to 12 wherein the pharmaceutically acceptable salt is a sodium, potassium, magnesium, calcium, or ammonium salt.

14. A pharmaceutical composition as claimed in any of claims 1 to 12 wherein the pharmaceutically acceptable salt is a salt with an organic base.

15. A pharmaceutical composition as claimed in claim 14 wherein the organic base is selected from triethanolamine, diethylaminoethylamine, piperazine and morpholine.

16. A pharmaceutical composition as claimed in any of claims 1 to 15 wherein the pharmaceutical composition is formulated for oral or rectal administration.

17. A pharmaceutical composition as claimed in claim 16 characterised in that the pharmaceutical composition is presented in unit dosage form.

18. A pharmaceutical composition as claimed in claim 17 wherein the pharmaceutical composition is presented in the form of a table or in a capsule.

19. A pharmaceutical composition as claimed in either of claims 17 and 18 wherein the pharmaceutical composition is presented as a moisture resistant formulation such as a coated tablet or in a capsule.

20. A pharmaceutical composition as claimed in any of claims 17 to 19 wherein each unit contains from 50 to 500 mg. of the tricyclic compound.

21. A pharmaceutical composition as claimed in any of claims 1 to 15 wherein the tricyclic compound is in the form of a finely comminuted powder for pulmonary administration.

22. A pharmaceutical composition as claimed in claim 21 wherein the pharmaceutically acceptable carrier includes a surfactant.

23. A pharmaceutical composition as claimed in either of claims 21 and 22 wherein the carrier includes a liquid medium.

24. A pharmaceutical composition as claimed in any of claims 21 to 23 wherein the pharmaceutical composition is a self-propelling aerosol composition in a sealed valved container.

25. A pharmaceutical composition as claimed in claim 24 wherein the tricyclic compound comprises from 0.1 to 20% w/w of the pharmaceutical composition.

26. A pharmaceutical composition as claimed in either of claims 24 and 25 wherein the propellent is selected from the class of lower alkyl hydrocarbons and halogenated lower alkyl hydrocarbons.

27. A pharmaceutical composition as claimed in any of claims 24 to 26 wherein the propelllent has a boiling point below 18°C at atmospheric pressure and comprises from 50 to 99.9% w/w of the pharmaceutical composition.

28. A pharmaceutical composition as claimed in any of claims 24 to 27 wherein the composition includes from 0.01 to 20% w/w of a surfactant.

29. A pharmaceutical composition as claimed in either of claims 21 and 22 wherein the pharmaceutical composition is free of liquid carrier.

30. A pharmaceutical composition as claimed in claim 29 wherein the tricyclic compound finely comminuted powder is presented in a capsule for use in an antihalation device.

31. A pharmaceutical composition as claimed in either of claims 29 and 30 wherein the carrier includes particles of a sugar.

32. A pharmaceutical composition as claimed in any of claims 21, 22 and 29 to 31 wherein the tricyclic compound finely comminuted powder comprises up to 99.9% w/w of the composition.

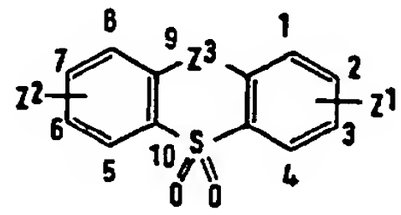
33. A pharmaceutical composition as claimed in any of claims 21 to 32 wherein at least 95% by number of the tricyclic compound finely comminuted powder particles have a diameter less than 7μ.

34. A pharmaceutical composition as claimed in any of claims 21 to 33 wherein at least 98% by weight of the tricyclic compound finely comminuted powder particles have a diameter greater than 0.5μ.

35. A method of preparing a pharmaceutical composition as claimed in any of claims 1 to 34 wherein the tricyclic compound is brought into intimate admixture with the pharmaceutically acceptable carrier.

36. A method of preparing a pharmaceutical composition as claimed in any of claims 24 to 28 wherein the tricyclic compound, as a finely comminuted suspension in a suitable liquid, is mixed with any other constituent(s) of a pharmaceutically acceptable carrier; the resulting mixture is cooled and introduced into a suitable cooled container; propellent is added thereto in liquid form and the container is sealed.

37. Tricyclic compounds of formula (I)



(I)

wherein Z^1 is a substituent in the 1, 2-, 3-, or 4-position and is carboxyl, a carboxylate salt group, an alkyl carboxylate group having 1 to 6 carbon atoms in the alkyl moiety, or a

carboxamide group optionally *N*-substituted by alkyl having 1 to 6 carbon atoms;

Z^3 represents a bond or is carbonyl, oxygen, sulphur, sulphoxide or methylene; and

Z^2 is a hydrogen or a substituent in the 5-, 6-, 7- or 8-position selected from a carboxylate salt group, alkylsulphonyl, alkylsulphinyl, alkylthio, amino, alkanoylamino, nitro, cyano, halogen, alkanoyl, alkyl, and alkoxy wherein the "alkyl" moiety of each of the alkanoyl, alkyl, alkoxy, alkylthio, alkanoylamino, alkylsulphinyl and alkylsulphonyl groups has 1 to 6 carbon atoms; provided that when Z^2 is hydrogen or a carboxylate salt group then Z^1 is always a carboxylate salt group and the compounds of formula (I) are in the solid state; and provided that, when Z^3 is carbonyl and Z^1 is in the 2-positon then Z^2, when a substituent in the 5-, 6- or 7-position, is other than halogen, alkanoyl, alkyl, alkoxy, alkylthio, alkylsulphinyl and alkylsulphonyl, and except for 7 - nitro - 2 - carboxythioxanthone - 10,10 - dioxide and its amide, 9 - nitro - 4 - carboxyphenoxathiin - 10,10 - dioxide, 8 - chloro - 2 - carboxyphenoxathiin - 10,10 - dioxide and its methyl ester, 4,6 - dicarboxydibenzothiophene - 5,5 - dioxide disodium salt, and 8 - chloro - 2 - carboxythioxanthone - 10,10 - dioxide.

38. A tricyclic compound as claimed in claim 37 wherein Z^1 is in the 3-position.

39. A tricyclic compound as claimed in claim 38 wherein Z^1 is carboxyl or a carboxylate salt group.

40. A tricyclic compound as claimed in claim 37 wherein Z^3 is oxygen, carbonyl or sulphur.

41. A tricyclic compound as claimed in claim 40 wherein Z^2 is selected from chlorine, nitro, methyl and methoxy.

42. A tricyclic compound as claimed in claim 41 wherein Z^2 is in the 7-position.

43. Tricyclic compounds of formula (I) according to claim 37 in the solid state wherein Z^1 is a substituent in the 1-, 2-, 3-, or 4-position and is a pharmaceutically acceptable carboxylate salt group; Z^2 is hydrogen or a substituent in the 5-, 6-, 7-, or 8-position selected from a pharmaceutically acceptable carboxylate salt group, alkylsulphonyl, alkylsulphinyl, alkylthio, amino, alkanoylamino, nitro, cyano, halogen, alkanoyl, alkyl and alkoxy wherein the "alkyl" moiety of each of the alkyl, alkanoyl, alkoxy, alkylthio, alkanoylamino, alkylsulphinyl and alkylsulphonyl groups has 1 to 6 carbon atoms; and Z^3 represents a bond or is a carbonyl, oxygen, sulphur, sulphoxide or methylene; provided that, when Z^3 is carbonyl and Z^1 is in the 2-position then Z^2, when a substituent in the 5-, 6- or 7-position, is other than halogen, alkanoyl, alkyl, alkoxy, alkylthio, alkylsulphinyl and alkylsulphonyl, and except for 4,6-dicarboxy - dibenzothiophene - 5,5 - dioxide disodium salt.

44. Tricyclic compounds according to claim 43 wherein Z^2 is hydrogen.

45. A compound as claimed in any of claims 37 to 44 when in the form of solid particles.

46. A compound as claimed in claim 45 wherein at least 95% by number of the particles have a diameter less than 7μ.

47. A compound as claimed in either of claims 45 and 46 wherein at least 98% by weight of the particles have a diameter greater than 0.5μ.

48. Salts of 3 - carboxythioxanthone - 10,10 - dioxide in the solid state.

49. Pharmaceutically acceptable salts of 3 - carboxythioxanthone - 10,10 - dioxide in the solid state.

50. Sodium, potassium and ammonium salts of 3 - carboxythioxanthone - 10,10 - dioxide in the solid state.

51. 3 - Carboxythioxanthone - 10,10 - dioxide sodium salt in the solid state.

52. 3 - Carboxy - 7 - chlorothioxanthone - 10,10 - dioxide.

53. 3 - Carboxy - 7 - methoxythioxanthone - 10,10 - dioxide.

54. 3 - Carboxy - 7 - nitrothioxanthone - 10,10 - dioxide.

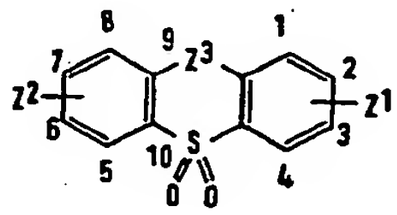
55. 3 - Carboxy - 7 - methylthioxanthone - 10,10 - dioxide.

56. 3 - Carboxy - 7 - ethylthioxanthone - 10,10 - dioxide.

57. 7 - tert.Butyl - 3 - carboxythioxanthone - 10,10 - dioxide.

58. 2 - Carboxy - 8 - methylphenoxathiin - 10,10 - dioxide.

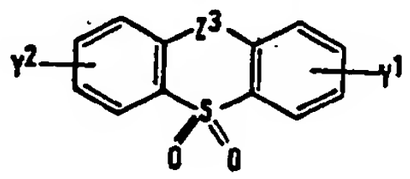
59. A method of preparing a tricyclic compound of formula (I) as claimed in any of claims 37 to 44



(I)

wherein Z^1, Z^2 and Z^3 have the meaning according to any of said claims, characterised in that:

a) when Z^1 is carboxyl or a carboxylate salt group or both Z^1 and Z^2 are carboxylate salt groups, a compound of formula (XIX)

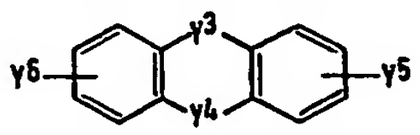


(XIX)

wherein Z^3 has the same meaning as above in formula (I); Y^1 is a carboxyl group precursor or a group Z^1 as defined above in formula (I); and Y^2 is a carboxyl group precursor or a group Z^2 as defined above in formula (I), provided that at least one of Y^1

and Y^3 is a carboxyl group precursor is hydrolysed with a base or with a dilute aqueous mineral acid optionally in the presence of an organic acid; and as appropriate and as desired the product is converted to the carboxyl compound or a salt thereof.

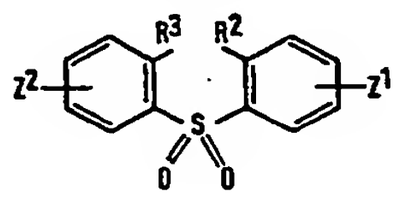
b) a compound of formula (XXI)



(XXI)

wherein Y^5 is an alkyl group, an alkanoyl group, or a group Z^1 as defined hereinabove in formula (I), Y^3 represents a bond or is carbonyl, oxygen, sulphur, sulphoxide or methylene; Y^4 is sulphur, sulphoxide or sulphone and Y^6 is an alkyl group, an alkanoyl group, or a group Z^3 as defined hereinebove in formula (I) provided that when Y^5 is the same as Z^1 and Y^6 is the same as Z^2 then at least Y^4 is sulphur or sulphoxide or Y^3 is methylene or sulphur is oxidised with an appropriate oxidising agent;

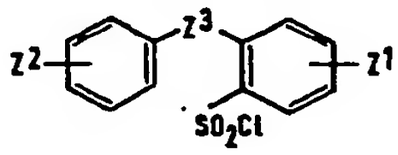
c) when Z^3 is oxygen or sulphur a compound of formula (XVI)



(XVI)

wherein Z^1 and Z^2 each have the same meaning as above in formula (I); one of R^2 and R^3 is a mercapto, hydroxy, or ester thereof and the other is a leaving group is cyclised using a base;

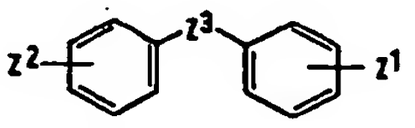
d) a compound of formula (XIV)



(XIV)

wherein Z^1, Z^2 and Z^3 have the same meaning as above in formula (I) is cyclised using a Lewis acid;

e) a compound of formula (XIII)

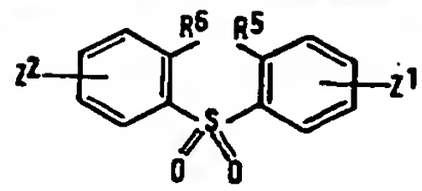


(XIII)

wherein Z^1, Z^2 and Z^3 have the same meaning as above in formula (I) is cyclised with chlorosulphonic acid;

f) when Z^3 is sulphur or methylene the corresponding compound of formula (I) wherein Z^3 is sulphoxide or carbonyl, respectively, is reduced with an appropriate reducing agent;

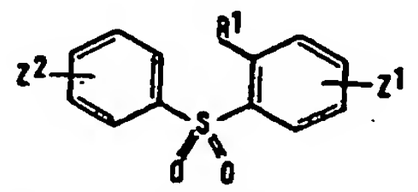
g) when Z^3 is sulphur a compound of formula (XVII)



(XVII)

wherein Z^1 and Z^2 have the same meaning as above in formula (I) and R^5 and R^6 are the same or different and each is a leaving group, is reacted with sodium sulphide; or

h) when Z^3 is carbonyl a compound of formula (XV)



(XV)

wherein Z^1 and Z^2 have the same meaning as above in formula (I) and R^1 is a carboxyl group, a derivative thereof or an aldehyde is cyclised in the presence of a Lewis or protonic acid; to provide a tricyclic compound of formula (I); and as required said compound is isolated in the solid state; and where a pharmaceutically acceptable carboxylate salt, an alkyl carboxylate or a carboxamide compound of formula (I) is required, the product of any of the above reactions is converted to the corresponding pharmaceutically acceptable carboxylate salt, alkyl carboxylate or carboxamide compound as defined in formula (I).

60. A method as claimed in claim 59 characterised in that the reaction to provide the tricyclic compound is effected in a liquid medium.

61. A method as claimed in Claim 59a, characterised in that the carboxyl group precursor is selected from a nitrile group, a trichloromethyl group and a group COL1 wherein L^1 is a leaving group.

62. A method as claimed in Claim 61 characterised in that the leaving group 1 is a nucleophilic group.

63. A method as claimed in Claim 62 characterised in that the nucleophilic group is selected from a trichloromethyl group, an optionally substituted amino group, a halogen atom and an alkoxy group.

64. A method as claimed in Claim 59b, characterised in that when Y^3 is methylene or at least one of Y^5 and Y^4 is an alkyl or alkanoyl group, the oxidising agent is selected from nitric acid; a dichromate salt in acetic acid aqueous solution; chromium trioxide optionally with acetic acid or sulphuric acid; oxygen in the presence of a conventional catalyst and acid or alkaline aqueous potassium permanganate.

65. A method as claimed in claim 64, characterised in that when at least one of Y^5 and Y^6 is an alkanoyl group and the other is not an alkyl group, the oxidising agent is

also selected from nitric acid and from aqueous solutions of salts of hypochlorous or hypobromous acid in the presence of a base.

66. A method as claimed in claim 59b, characterised in that when Y^4 is sulphur or sulphoxide and/or Y^3 is sulphur, the oxidising agent is hydrogen peroxide in the presence of acetic acid.

67. A method as claimed in claim 59c, characterised in that the base is an alkali metal alkoxide.

68. A method as claimed in Claim 67 characterised in that the base is sodium methoxide.

69. A method as claimed in either of claims 67 and 68 characterised in that the leaving group is selected from a nitro group, a sulphinyl group and a halogen atom.

70. A method as claimed in claim 59d characterised in that the Lewis acid is aluminium trichloride.

71. A method as claimed in claim 59f, characterised in that the reducing agent is zinc in the presence of an acid.

72. A method as claimed in claim 71 characterised in that the acid is selected from hydrochloric and acetic acids.

73. A method as claimed in claim 59g, characterised in that the leaving groups are each selected from a nitro group, a sulphinyl group and a halogen atom.

74. A method as claimed in claim 59h characterised in that the carboxyl derivative is selected from a nitrile group, an amide group and an acid chloride group.

75. A method as claimed in either of claims 59h and 74 characterised in that the protonic acid is sulphuric acid or polyphosphoric acid.

76. A method as claimed in either of claims 59h and 74 characterised in that the Lewis acid is boron trifluoride or aluminium trichloride.

77. A tricyclic compound defined in any of claims 37 to 44 when prepared by the process defined in the appropriate claim selected from claims 59 to 76.

78. A pharmaceutical composition of a tricyclic compound of formula (I) as defined in claim 1, substantially as herein described.

79. A pharmaceutical composition of a tricyclic compound of formula (I) as defined in claim 1, substantially as hereinbefore described with particular reference to the accompanying Examples.

80. A process of preparing a tricyclic compound of formula (I) as defined in claim 59, substantially as hereinbefore described with particular reference to the accompanying Examples.

81. A process of preparing a tricyclic compound of formula (I) which is the end-product of at least one of the accompanying Examples substantially as hereinbefore described in said Examples.

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